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(57) Abstract Compounds containing two aromatic systems covalently linked through a linker containing one or more atoms, or "linker" defined as including a covalent bond <i>per se</i> so as to space the aromatic systems at a distance 1.5–15 Å, are effective in treating conditions associated with bone deficits. The compounds can be administered to vertebrate subjects alone or in combination with additional agents that promote bone growth or that inhibit bone resorption. They can be screened for activity prior to administration by assessing their ability to effect the transcription of a reporter gene coupled to a promoter associated with a bone morphogenetic protein and/or their ability to stimulate calvarial growth in model animal systems.			

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COMPOSITIONS AND METHODS FOR TREATING BONE DEFICIT CONDITIONS

Technical Field

5 The invention relates to compositions and methods for use in limiting undesired bone loss in a vertebrate at risk of such bone loss, in treating conditions that are characterized by undesired bone loss or by the need for bone growth, in treating fractures, and in treating cartilage disorders. More specifically, the invention concerns the use of specific classes of compounds identified or characterized by a high
10 throughput screening assay.

Background Art

Bone is not a static tissue. It is subject to constant breakdown and resynthesis in a complex process mediated by osteoblasts, which produce new bone, and
15 osteoclasts, which destroy bone. The activities of these cells are regulated by a large number of cytokines and growth factors, many of which have now been identified and cloned. Mundy has described the current knowledge related to these factors (Mundy, G.R. *Clin Orthop* 324:24-28, 1996; Mundy, G.R. *J Bone Miner Res* 8:S505-10, 1993).

20 Although there is a great deal of information available on the factors which influence the breakdown and resorption of bone, information on growth factors which stimulate the formation of new bone is more limited. Investigators have searched for sources of such activities, and have found that bone tissue itself is a storehouse for factors which have the capacity for stimulating bone cells. Thus, extracts of bovine
25 bone tissue obtained from slaughterhouses contain not only structural proteins which are responsible for maintaining the structural integrity of bone, but also biologically active bone growth factors which can stimulate bone cells to proliferate. Among these latter factors are transforming growth factor β , the heparin-binding growth factors (acidic and basic fibroblast growth factor), the insulin-like growth factors (insulin-like
30 growth factor I and insulin-like growth factor II), and a recently described family of

proteins called bone morphogenetic proteins (BMPs). All of these growth factors have effects on other types of cells, as well as on bone cells.

The BMPs are novel factors in the extended transforming growth factor β superfamily. They were first identified by Wozney J. *et al. Science* (1988) 242:1528-34, using gene cloning techniques, following earlier descriptions characterizing the biological activity in extracts of demineralized bone (Urist M. *Science* (1965) 150:893-99). Recombinant BMP2 and BMP4 can induce new bone formation when they are injected locally into the subcutaneous tissues of rats (Wozney J. *Molec Reprod Dev* (1992) 32:160-67). These factors are expressed by normal osteoblasts as they 10 differentiate, and have been shown to stimulate osteoblast differentiation and bone nodule formation *in vitro* as well as bone formation *in vivo* (Harris S. *et al. J. Bone Miner Res* (1994) 9:855-63). This latter property suggests potential usefulness as therapeutic agents in diseases which result in bone loss.

The cells which are responsible for forming bone are osteoblasts. As 15 osteoblasts differentiate from precursors to mature bone-forming cells, they express and secrete a number of enzymes and structural proteins of the bone matrix, including Type-1 collagen, osteocalcin, osteopontin and alkaline phosphatase (Stein G. *et al. Curr Opin Cell Biol* (1990) 2:1018-27; Harris S. *et al.* (1994), *supra*). They also synthesize a number of growth regulatory peptides which are stored in the bone matrix, 20 and are presumably responsible for normal bone formation. These growth regulatory peptides include the BMPs (Harris S. *et al.* (1994), *supra*). In studies of primary cultures of fetal rat calvarial osteoblasts, BMPs 1, 2, 3, 4, and 6 are expressed by cultured cells prior to the formation of mineralized bone nodules (Harris S. *et al.* (1994), *supra*). Like alkaline phosphatase, osteocalcin and osteopontin, the BMPs are 25 expressed by cultured osteoblasts as they proliferate and differentiate.

Although the BMPs are potent stimulators of bone formation *in vitro* and *in vivo*, there are disadvantages to their use as therapeutic agents to enhance bone healing. Receptors for the bone morphogenetic proteins have been identified in many tissues, and the BMPs themselves are expressed in a large variety of tissues in specific 30 temporal and spatial patterns. This suggests that BMPs may have effects on many

tissues other than bone, potentially limiting their usefulness as therapeutic agents when administered systemically. Moreover, since they are peptides, they would have to be administered by injection. These disadvantages impose severe limitations to the development of BMPs as therapeutic agents.

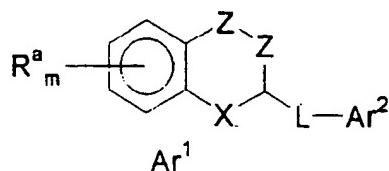
5 There is a plethora of conditions which are characterized by the need to enhance bone formation. Perhaps the most obvious is the case of bone fractures, where it would be desirable to stimulate bone growth and to hasten and complete bone repair. Agents that enhance bone formation would also be useful in facial reconstruction procedures. Other bone deficit conditions include bone segmental
10 defects, periodontal disease, metastatic bone disease, osteolytic bone disease and conditions where connective tissue repair would be beneficial, such as healing or regeneration of cartilage defects or injury. Also of great significance is the chronic condition of osteoporosis, including age-related osteoporosis and osteoporosis associated with postmenopausal hormone status. Other conditions characterized by
15 the need for bone growth include primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. In addition, or alternatively, the compounds of the present invention may modulate metabolism, proliferation and/or differentiation of normal or aberrant cells or tissues.

There are currently no satisfactory pharmaceutical approaches to managing any
20 of these conditions. Bone fractures are still treated exclusively using casts, braces, anchoring devices and other strictly mechanical means. Further bone deterioration associated with postmenopausal osteoporosis has been decreased or prevented with estrogens or bisphosphonates.

US Patent 5, 280, 040 discloses a class of compounds which are 3, 4-diaryl
25 chromans. These compounds can be considered derivatives of 2,3,4 triphenyl butanol, where the hydroxy at the 1-position forms an ether with the ortho position of the phenyl group substituted at the 4-position of the butanol. The parent 3,4-diaryl chromans do not contain nitrogen atoms in the aromatic moieties or their linkers. A preferred compound, centchroman, contains a nitrogen substituent only in one of the

substituents on a phenyl moiety. These compounds are disclosed in the '040 patent as useful in the treatment of osteoporosis.

In addition, the PCT application WO97/15308 published 1 May 1997 describes a number of classes of compounds that are active in the screening assay described 5 below and are useful in treating bone disorders. These compounds, generically, are of the formulae



wherein R^a is a non-interfering substituent;

10 m is an integer of 0-4;

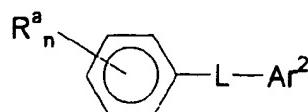
each dotted line represents an optional π-bond;

each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO₂;

15 L is a flexible linker; and

Ar² is a substituted or unsubstituted 6-membered aromatic ring; or:



wherein R^a is a non-interfering substituent;

n is an integer of 0 and 5;

20 L is a flexible linker which does not contain nitrogen or is a constrained linker; and

Ar² is a substituted or unsubstituted phenyl or a substituted or unsubstituted naphthyl.

There remains a need for additional compositions which can ameliorate the 25 effects of abnormalities in bone formation or resorption. The present invention

expands the repertoire of compounds useful for limiting or treating bone deficit conditions, and for other uses that should be apparent to those skilled in the art from the teachings herein.

5 Disclosure of the Invention

The invention provides compounds that can be administered as ordinary pharmaceuticals and have the metabolic effect of enhancing bone growth or inhibiting resorption. The compounds of the invention can be identified using an assay for their ability to activate control elements associated with bone anabolic factors. Thus, the
10 invention is directed to methods and compositions for treating bone disorders, which methods and compositions use, as active ingredients, compounds wherein two aromatic systems are coupled so as to be spaced apart from each other by about 1.5 to about 15 Angstroms. The thus-linked systems (including the linker coupling them) preferably include at least one nitrogen atom.

15 Therefore, the compounds useful in the invention can be described as having the formula Ar¹-linker-Ar², wherein each of Ar¹ and Ar² is independently an aromatic system and the linker portion of the formula spaces Ar¹ and Ar² apart by a distance of approximately 1.5-15 Angstroms. Ar¹, Ar² and the linker may optionally be substituted with non interfering substituents. In the useful compounds, there is
20 preferably at least one nitrogen atom in either Ar¹, Ar² and/or the linker, independent of any substituents thereon. Preferably, the compounds of the invention contain at least one additional heteroatom selected from the group consisting of N, S and O, independent of any substituent.

Thus, in one aspect, the invention is directed to a method to treat a condition in
25 a vertebrate animal characterized by a deficiency in, or need for, bone growth replacement and/or an undesirable level of bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of certain compounds of the formula:



wherein each of Ar¹ and Ar² is independently substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, a substituted or unsubstituted aromatic system containing a 6-membered heterocycle, or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and

5 L is a linker that provides spacing of 1.5-15Å.

In other aspects, the invention relates to pharmaceutical compositions for use in the method, and to the compounds for use in preparing a medicament for use in the method.

10 Brief Description of the Drawings

Figure 1 gives a schematic representation of the compounds used as active ingredients in the methods and compositions of the invention.

Figure 2 shows the dose response curve for a positive control compound, designated 59-0008.

15 Figures 3 and 4 show illustrative compounds of the invention and the results obtained with them in an *in vitro* test for stimulation of bone growth.

Figures 5A, 5B and 5C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0072.

20 Figures 6A, 6B and 6C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 50-0197.

Figure 7 shows structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0145.

Figures 8A, 8B and 8C show structures and results of a screening assay for a group of compounds which varies the parameters of lead compound 59-0045.

25 Figure 9 shows the results in an *ex vivo* calvarial assay for various compounds of the invention.

Figure 10 shows the increase in bone volume effected by subcutaneous administration of compound 59-0145 in the OVX *in vivo* assay.

30 Figure 11 is a graphical representation of percent increase in trabecular bone in ovariectomized rats treated with compound 59-0145.

Figure 12 presents graphs showing results of qCT and bone histomorphometry and serum osteocalcin levels in rats treated with compound 59-0145.

Figure 13 (41 pages) is a list of compounds used in screening for bone morphogenic activity according to the screening assay set forth herein.

5

Modes of Carrying Out the Invention

A rapid throughput screening test for compounds capable of stimulating expression of a reporter gene linked to a BMP promoter (a surrogate for the production of bone morphogenetic factors that are endogenously produced) is 10 described in WO96/38590 published 5 December 1996, the contents of which are incorporated herein by reference. This assay is also described as a portion of a study of immortalized murine osteoblasts (derived from a mouse expressing a transgene composed of a BMP2 promoter driving expression of T-antigen) in Ghosh-Choudhury, N. *et al. Endocrinology* (1996) 137:331-39. In this study, the immortalized cells were 15 stably transfected with a plasmid containing a luciferase reporter gene driven by a mouse BMP2 promoter (-2736/114 bp), and responded in a dose-dependent manner to recombinant human BMP2.

Briefly, the assay utilizes cells transformed permanently or transiently with constructs in which the promoter of a bone morphogenetic protein, specifically BMP2 20 or BMP4, is coupled to a reporter gene, typically luciferase. These transformed cells are then evaluated for the production of the reporter gene product; compounds that activate the BMP promoter will drive production of the reporter protein, which can be readily assayed. Over 40,000 compounds have been subjected to this rapid screening technique, and only a very small percentage are able to elicit a level of production of 25 luciferase 5-fold greater than that produced by vehicle. Compounds that activate the BMP promoter share certain structural characteristics not present in inactive compounds. The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth.

BMP promoter-active compounds can be examined in a variety of other assays that test specificity and toxicity. For instance, nonBMP promoters or response elements can be linked to a reporter gene and inserted into an appropriate host cell.

Cytotoxicity can be determined by visual or microscopic examination of BMP

- 5 promoter- and/or nonBMP promoter-reporter gene-containing cells, for instance. Alternatively, nucleic acid and/or protein synthesis by the cells can be monitored. For *in vivo* assays, tissues may be removed and examined visually or microscopically, and optionally examined in conjunction with dyes or stains that facilitate histologic examination. In assessing *in vivo* assay results, it may also be useful to examine
- 10 biodistribution of the test compound, using conventional medicinal chemistry/animal model techniques.

As used herein, "limit" or "limiting" and "treat" or "treatment" are interchangeable terms. The terms include a postponement of development of bone deficit symptoms and/or a reduction in the severity of such symptoms that will or are

- 15 expected to develop. The terms further include ameliorating existing bone or cartilage deficit symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, preventing or reversing bone resorption and/or encouraging bone growth. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a cartilage, bone or skeletal deficit, or with
- 20 the potential to develop such deficit.

By "bone deficit" is meant an imbalance in the ratio of bone formation to bone resorption, such that, if unmodified, the subject will exhibit less bone than desirable, or the subject's bones will be less intact and coherent than desired. Bone deficit may also result from fracture, from surgical intervention or from dental or periodontal disease.

- 25 By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or cartilage that is less intact and coherent than desired.

Representative uses of the compounds of the present invention include: repair of bone defects and deficiencies, such as those occurring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone

- 30 healing in plastic surgery; stimulation of bone ingrowth into noncemented prosthetic

joints and dental implants; elevation of peak bone mass in premenopausal women; treatment of growth deficiencies; treatment of periodontal disease and defects, and other tooth repair processes; increase in bone formation during distraction osteogenesis; and treatment of other skeletal disorders, such as age-related osteoporosis, postmenopausal 5 osteoporosis, glucocorticoid-induced osteoporosis or disuse osteoporosis and arthritis.

The compounds of the present invention can also be useful in repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery. Further, the compounds of the present invention can be used for limiting or treating cartilage defects or disorders, and may be useful in wound healing 10 or tissue repair.

Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention which have been identified through suitable screening assays and which exhibit certain structural characteristics. The compositions of the invention may be administered systemically or locally. For systemic use, the 15 compounds herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration will be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration will generally be 20 performed at intervals ranging from weekly to once to three times daily. Alternatively, the compounds disclosed herein may be administered in a cyclical manner (administration of disclosed compound; followed by no administration; followed by administration of disclosed compound, and the like). Treatment will continue until the desired outcome is achieved. In general, pharmaceutical formulations will include a 25 compound of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, borate-buffered saline containing trace metals or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, lubricants, fillers, stabilizers, etc. Methods of formulation are well 30 known in the art and are disclosed, for example, in Remington's Pharmaceutical

Sciences, Gennaro, ed., Mack Publishing Co., Easton PA, 1990, which is incorporated herein by reference. Pharmaceutical compositions for use within the present invention can be in the form of sterile, nonpyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art. Local administration may be by injection at the site of injury or defect, or by insertion or attachment of a solid carrier at the site, or by direct, topical application of a viscous liquid. For local administration, the delivery vehicle preferably provides a matrix for the growing bone or cartilage, and more preferably is a vehicle that can be absorbed by the subject without adverse effects.

Delivery of compounds herein to wound sites may be enhanced by the use of controlled-release compositions, such as those described in WIPO publication WO 93/20859, which is incorporated herein by reference in its entirety. Films of this type are particularly useful as coatings for prosthetic devices and surgical implants. The films may, for example, be wrapped around the outer surfaces of surgical screws, rods, pins, plates and the like. Implantable devices of this type are routinely used in orthopedic surgery. The films can also be used to coat bone filling materials, such as hydroxyapatite blocks, demineralized bone matrix plugs, collagen matrices and the like. In general, a film or device as described herein is applied to the bone at the fracture site. Application is generally by implantation into the bone or attachment to the surface using standard surgical procedures.

In addition to the copolymers and carriers noted above, the biodegradable films and matrices may include other active or inert components. Of particular interest are those agents that promote tissue growth or infiltration, such as growth factors. Exemplary growth factors for this purpose include epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factors (TGFs), parathyroid hormone (PTH), leukemia inhibitory factor (LIF), and insulin-like growth factors (IGFs). Agents that promote bone growth, such as bone morphogenetic proteins (U.S. Patent No. 4,761,471; PCT Publication WO 90/11366), osteogenin (Sampath *et al. Proc. Natl. Acad. Sci. USA* (1987) 84:7109-13) and NaF (Tencer *et al. J. Biomed. Mat. Res.* (1989) 23: 571-89) are also preferred.

Biodegradable films or matrices include calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyanhydrides, bone or dermal collagen, pure proteins, extracellular matrix components and combinations thereof. Such biodegradable materials may be used in combination with nonbiodegradable materials, 5 to provide desired mechanical, cosmetic or tissue or matrix interface properties.

Alternative methods for delivery of compounds of the present invention include use of ALZET osmotic minipumps (Alza Corp., Palo Alto, CA); sustained release matrix materials such as those disclosed in Wang *et al.* (PCT Publication WO 90/11366); electrically charged dextran beads, as disclosed in Bao *et al.* (PCT 10 Publication WO 92/03125); collagen-based delivery systems, for example, as disclosed in Ksander *et al.* *Ann. Surg.* (1990) 211(3):288-94; methylcellulose gel systems, as disclosed in Beck *et al.* *J. Bone Min. Res.* (1991) 6(11):1257-65; and alginate-based systems, as disclosed in Edelman *et al.* *Biomaterials* (1991) 12:619-26. Other 15 methods well known in the art for sustained local delivery in bone include porous coated metal prostheses that can be impregnated and solid plastic rods with therapeutic compositions incorporated within them.

The compounds of the present invention may also be used in conjunction with agents that inhibit bone resorption. Antiresorptive agents, such as estrogen, bisphosphonates and calcitonin, are preferred for this purpose. More specifically, the 20 compounds disclosed herein may be administered for a period of time (for instance, months to years) sufficient to obtain correction of a bone deficit condition. Once the bone deficit condition has been corrected, the vertebrate can be administered an anti-resorptive compound to maintain the corrected bone condition. Alternatively, the compounds disclosed herein may be administered with an anti-resorptive compound in 25 a cyclical manner (administration of disclosed compound, followed by anti-resorptive, followed by disclosed compound, and the like).

In additional formulations, conventional preparations such as those described below may be used.

Aqueous suspensions may contain the active ingredient in admixture with 30 pharmacologically acceptable excipients, comprising suspending agents, such as methyl

cellulose; and wetting agents, such as lecithin, lysolethicin or long-chain fatty alcohols. The said aqueous suspensions may also contain preservatives, coloring agents, flavoring agents and sweetening agents in accordance with industry standards.

Preparations for topical and local application comprise aerosol sprays, lotions, 5 gels and ointments in pharmaceutically appropriate vehicles which may comprise lower aliphatic alcohols, polyglycols such as glycerol, polyethylene glycol, esters of fatty acids, oils and fats, and silicones. The preparations may further comprise antioxidants, such as ascorbic acid or tocopherol, and preservatives, such as p-hydroxybenzoic acid esters.

10 Parenteral preparations comprise particularly sterile or sterilized products. Injectable compositions may be provided containing the active compound and any of the well known injectable carriers. These may contain salts for regulating the osmotic pressure.

If desired, the osteogenic agents can be incorporated into liposomes by any of 15 the reported methods of preparing liposomes for use in treating various pathogenic conditions. The present compositions may utilize the compounds noted above incorporated in liposomes in order to direct these compounds to macrophages, monocytes, other cells and tissues and organs which take up the liposomal composition. The liposome-incorporated compounds of the invention can be utilized 20 by parenteral administration, to allow for the efficacious use of lower doses of the compounds. Ligands may also be incorporated to further focus the specificity of the liposomes.

Suitable conventional methods of liposome preparation include, but are not limited to, those disclosed by Bangham, A.D. *et al. J Mol Biol* (1965) 23:238-252, 25 Olson, F. *et al. Biochim Biophys Acta* (1979) 557:9-23, Szoka, F. *et al. Proc Natl Acad Sci USA* (1978) 75:4194-4198, Mayhew, E. *et al. _____* (1984) 775:169-175, Kim, S. *et al. Biochim Biophys Acta* (1983) 728:339:348, and Mayer, *et al. Biochim Biophys Acta* (1986) 858:161-168.

The liposomes may be made from the present compounds in combination with 30 any of the conventional synthetic or natural phospholipid liposome materials including

phospholipids from natural sources such as egg, plant or animal sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, sphingomyelin, phosphatidylserine, or phosphatidylinositol. Synthetic phospholipids that may also be used, include, but are not limited to: dimyristoylphosphatidylcholine,
5 dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine, and the corresponding synthetic phosphatidylethanolamines and phosphatidylglycerols. Cholesterol or other sterols, cholesterol hemisuccinate, glycolipids, cerebrosides, fatty acids, gangliosides, sphingolipids, 1,2-bis(oleoyloxy)-3-(trimethyl ammonio) propane (DOTAP), N-[1-
10 (2,3-dioleoyl) propyl-N,N,N-trimethylammonium chloride (DOTMA), and other cationic lipids may be incorporated into the liposomes, as is known to those skilled in the art. The relative amounts of phospholipid and additives used in the liposomes may be varied if desired. The preferred ranges are from about 60 to 90 mole percent of the phospholipid; cholesterol, cholesterol hemisuccinate, fatty acids or cationic lipids may
15 be used in amounts ranging from 0 to 50 mole percent. The amounts of the present compounds incorporated into the lipid layer of liposomes can be varied with the concentration of their lipids ranging from about 0.01 to about 50 mole percent.

Using conventional methods, approximately 20 to 30% of the compound present in solution can be entrapped in liposomes; thus, approximately 70 to 80% of
20 the active compound is wasted. In contrast, where the compound is incorporated into liposomes, virtually all of the compound is incorporated into the liposome, and essentially none of the active compound is wasted.

The liposomes with the above formulations may be made still more specific for their intended targets with the incorporation of monoclonal antibodies or other ligands
25 specific for a target. For example, monoclonal antibodies to the BMP receptor may be incorporated into the liposome by linkage to phosphatidylethanolamine (PE) incorporated into the liposome by the method of Leserman, L. *et al. Nature* (1980)
288:602-604.

Veterinary uses of the disclosed compounds are also contemplated. Such uses
30 would include limitation or treatment of bone or cartilage deficits or defects in

domestic animals, livestock and thoroughbred horses. The compounds described herein can also modify a target tissue or organ environment, so as to attract bone-forming cells to an environment in need of such cells.

The compounds of the present invention may also be used to stimulate growth of bone-forming cells or their precursors, or to induce differentiation of bone-forming cell precursors, either *in vitro* or *ex vivo*. As used herein, the term "precursor cell" refers to a cell that is committed to a differentiation pathway, but that generally does not express markers or function as a mature, fully differentiated cell. As used herein, the term "mesenchymal cells" or "mesenchymal stem cells" refers to pluripotent progenitor cells that are capable of dividing many times, and whose progeny will give rise to skeletal tissues, including cartilage, bone, tendon, ligament, marrow stroma and connective tissue (see A. Caplan *J. Orthop. Res.* (1991) 9:641-50). As used herein, the term "osteogenic cells" includes osteoblasts and osteoblast precursor cells. More particularly, the disclosed compounds are useful for stimulating a cell population containing marrow mesenchymal cells, thereby increasing the number of osteogenic cells in that cell population. In a preferred method, hematopoietic cells are removed from the cell population, either before or after stimulation with the disclosed compounds. Through practice of such methods, osteogenic cells may be expanded. The expanded osteogenic cells can be infused (or reinfused) into a vertebrate subject in need thereof. For instance, a subject's own mesenchymal stem cells can be exposed to compounds of the present invention *ex vivo*, and the resultant osteogenic cells could be infused or directed to a desired site within the subject, where further proliferation and/or differentiation of the osteogenic cells can occur without immunorejection. Alternatively, the cell population exposed to the disclosed compounds may be immortalized human fetal osteoblastic or osteogenic cells. If such cells are infused or implanted in a vertebrate subject, it may be advantageous to "immunoprotect" these nonself cells, or to immunosuppress (preferably locally) the recipient to enhance transplantation and bone or cartilage repair.

Within the present invention, an "effective amount" of a composition is that amount which produces a statistically significant effect. For example, an "effective

- amount" for therapeutic uses is the amount of the composition comprising an active compound herein required to provide a clinically significant increase in healing rates in fracture repair; reversal of bone loss in osteoporosis; reversal of cartilage defects or disorders; prevention or delay of onset of osteoporosis; stimulation and/or
- 5 augmentation of bone formation in fracture nonunions and distraction osteogenesis; increase and/or acceleration of bone growth into prosthetic devices; and repair of dental defects. Such effective amounts will be determined using routine optimization techniques and are dependent on the particular condition to be treated, the condition of the patient, the route of administration, the formulation, and the judgment of the
- 10 practitioner and other factors evident to those skilled in the art. The dosage required for the compounds of the invention (for example, in osteoporosis where an increase in bone formation is desired) is manifested as a statistically significant difference in bone mass between treatment and control groups. This difference in bone mass may be seen, for example, as a 5-20% or more increase in bone mass in the treatment group.
- 15 Other measurements of clinically significant increases in healing may include, for example, tests for breaking strength and tension, breaking strength and torsion, 4-point bending, increased connectivity in bone biopsies and other biomechanical tests well known to those skilled in the art. General guidance for treatment regimens is obtained from experiments carried out in animal models of the disease of interest.
- 20 The dosage of the compounds of the invention will vary according to the extent and severity of the need for treatment, the activity of the administered compound, the general health of the subject, and other considerations well known to the skilled artisan. Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg, and more preferably from about 1 mg/kg to
- 25 about 200 mg/kg. The parenteral dose will appropriately be 20-100% of the oral dose.

Screening Assays

The osteogenic activity of the compounds used in the methods of the invention can be verified using *in vitro* screening techniques, such as the assessment of

transcription of a reporter gene coupled to a bone morphogenetic protein-associated promoter, as described above, or in alternative assays such as the following:

Technique for Neonatal Mouse Calvarial Assay (*In vitro*)

5 This assay is similar to that described by Gowen M. & Mundy G. *J Immunol* (1986) 136:2478-82. Briefly, four days after birth, the front and parietal bones of ICR Swiss white mouse pups are removed by microdissection and split along the sagittal suture. The bones are incubated in BGJb medium (Irvine Scientific, Santa Ana, CA) plus 0.02% (or lower concentration) β -methylcyclodextrin, wherein the medium also
10 contains test or control substances, at 37°C in a humidified atmosphere of 5% CO₂ and 95% air for 96 hours.

Following this, the bones are removed from the incubation media and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1 week, processed through graded alcohols; and embedded in paraffin wax. Three μ m sections
15 of the calvaria are prepared. Representative sections are selected for histomorphometric assessment of bone formation and bone resorption. Bone changes are measured on sections cut 200 μ m apart. Osteoblasts and osteoclasts are identified by their distinctive morphology.

Other auxillary assays can be used as controls to determine nonBMP promoter-mediated effects of test compounds. For example, mitogenic activity can be measured using screening assays featuring a serum-response element (SRE) as a promoter and a luciferase reporter gene. More specifically, these screening assays can detect signalling through SRE-mediated pathways, such as the protein kinase C pathway. For instance, an osteoblast activator SRE-luciferase screen and an insulin mimetic SRE-luciferase
20 screen are useful for this purpose. Similarly, test compound stimulation of cAMP response element (CRE)-mediated pathways can also be assayed. For instance, cells transfected with receptors for PTH and calcitonin (two bone-active agents) can be used in CRE-luciferase screens to detect elevated cAMP levels. Thus, the BMP promoter specificity of a test compound can be examined through use of these types of
25 auxillary assays.

In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth

Male ICR Swiss white mice, aged 4-6 weeks and weighing 13-26 gm, are employed, using 4-5 mice per group. The calvarial bone growth assay is performed as described in PCT application WO 95/24211. Briefly, the test compound or appropriate control vehicle is injected into the subcutaneous tissue over the right calvaria of normal mice. Typically, the control vehicle is the vehicle in which the compound was solubilized, and is PBS containing 5% DMSO or is PBS containing Tween (2 µl/10 ml). The animals are sacrificed on day 14 and bone growth measured by histomorphometry. Bone samples for quantitation are cleaned from adjacent tissues and fixed in 10% buffered formalin for 24-48 hours, decalcified in 14% EDTA for 1-3 weeks, processed through graded alcohols; and embedded in paraffin wax. Three to five µm sections of the calvaria are prepared, and representative sections are selected for histomorphometric assessment of the effects on bone formation and bone resorption. Sections are measured by using a camera lucida attachment to trace directly the microscopic image onto a digitizing plate. Bone changes are measured on sections cut 200 µm apart, over 4 adjacent 1x1 mm fields on both the injected and noninjected sides of the calvaria. New bone is identified by its characteristic woven structure, and osteoclasts and osteoblasts are identified by their distinctive morphology. Histomorphometry software (OsteoMeasure, Osteometrics, Inc., Atlanta) is used to process digitizer input to determine cell counts and measure areas or perimeters.

Additional In Vivo Assays

Lead compounds can be further tested in intact animals using an *in vivo*, dosing assay. Prototypical dosing may be accomplished by subcutaneous, intraperitoneal or oral administration, and may be performed by injection, sustained release or other delivery techniques. The time period for administration of test compound may vary (for instance, 28 days as well as 35 days may be appropriate). An exemplary, *in vivo* subcutaneous dosing assay may be conducted as follows:

In a typical study, 70 three-month-old female Sprague-Dawley rats are weight-matched and divided into seven groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; a control group administered vehicle only; a PBS-treated control group; and a positive control group administered a compound (nonprotein or protein) known to promote bone growth. 5 Three dosage levels of the compound to be tested are administered to the remaining three groups.

Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. All animals are injected with 10 calcein nine days and two days before sacrifice (two injections of calcein administered each designated day). Weekly body weights are determined. At the end of the 35-day cycle, the animals are weighed and bled by orbital or cardiac puncture. Serum calcium, phosphate, osteocalcin, and CBCs are determined. Both leg bones (femur and tibia) and lumbar vertebrae are removed, cleaned of adhering soft tissue, and stored in 70% 15 ethanol for evaluation, as performed by peripheral quantitative computed tomography (pqCT; Ferretti, *J. Bone* (1995) 17:353S-64S), dual energy X-ray absorptiometry (DEXA; Laval-Jeantet A. *et al. Calcif Tissue Intl* (1995) 56:14-18; J. Casez *et al. Bone and Mineral* (1994) 26:61-68) and/or histomorphometry. The effect of test compounds on bone remodeling can thus be evaluated.

20 Lead compounds also be tested in acute ovariectomized animals (prevention model) using an *in vivo* dosing assay. Such assays may also include an estrogen-treated group as a control. An exemplary subcutaneous dosing assay is performed as follows:

In a typical study, 80 three-month-old female Sprague-Dawley rats are weight-matched and divided into eight groups, with ten animals in each group. This includes a baseline control group of animals sacrificed at the initiation of the study; three control groups (sham ovariectomized (sham OVX) + vehicle only; ovariectomized (OVX) + vehicle only; PBS-treated OVX); and a control OVX group that is administered a 25 compound known to promote bone growth. Three dosage levels of the compound to 30 be tested are administered to the remaining three groups of OVX animals.

Since ovariectomy (OVX) induces hyperphagia, all OVX animals are pair-fed with sham OVX animals throughout the 35 day study. Briefly, test compound, positive control compound, PBS, or vehicle alone is administered subcutaneously once per day for 35 days. Alternatively, test compound can be formulated in implantable pellets that are implanted for 35 days, or may be administered orally, such as by gastric gavage. All animals, including sham OVX/vehicle and OVX/vehicle groups, are injected intraperitoneally with calcein nine days and two days before sacrifice (two injections of calcein administered each designated day, to ensure proper labeling of newly formed bone). Weekly body weights are determined. At the end of the 35-day cycle, the animals' blood and tissues are processed as described above.

Lead compounds may also be tested in chronic OVX animals (treatment model). An exemplary protocol for treatment of established bone loss in ovariectomized animals that can be used to assess efficacy of anabolic agents may be performed as follows. Briefly, 80 to 100 six month old female, Sprague-Dawley rats are subjected to sham surgery (sham OVX) or ovariectomy (OVX) at time 0, and 10 rats are sacrificed to serve as baseline controls. Body weights are recorded weekly during the experiment. After approximately 6 weeks of bone depletion (42 days), 10 sham OVX and 10 OVX rats are randomly selected for sacrifice as depletion period controls. Of the remaining animals, 10 sham OVX and 10 OVX rats are used as placebo-treated controls. The remaining OVX animals are treated with 3 to 5 doses of test drug for a period of 5 weeks (35 days). As a positive control, a group of OVX rats can be treated with an agent such as PTH, a known anabolic agent in this model (Kimmel *et al. Endocrinology* (1993) 132:1577-84). To determine effects on bone formation, the following procedure can be followed. The femurs, tibiae and lumbar vertebrae 1 to 4 are excised and collected. The proximal left and right tibiae are used for pqCT measurements, cancellous bone mineral density (BMD) (gravimetric determination), and histology, while the midshaft of each tibiae is subjected to cortical BMD or histology. The femurs are prepared for pqCT scanning of the midshaft prior to biomechanical testing. With respect to lumbar vertebrae (LV), LV2 are processed

for BMD (pqCT may also be performed); LV3 are prepared for undecalcified bone histology; and LV4 are processed for mechanical testing.

Nature of the Compounds Useful in the Invention

5 All of the compounds of the invention contain two aromatic systems, Ar¹ and Ar², spaced apart by a linker at a distance of 1.5-15 Å, and may preferably contain at least one nitrogen atom. A summary of the structural features of the compounds included within the invention is shown in Figure 1.

As shown, Ar¹ and Ar² may include various preferred embodiments. These are
10 selected from the group consisting of a substituted or unsubstituted aromatic ring system containing a 5-membered heterocycle; a substituted or unsubstituted aromatic ring system containing a six-membered heterocycle; a substituted or unsubstituted naphthalene moiety; and a substituted or unsubstituted benzene moiety. There are 16 possible combinations of these embodiments, if Ar¹ and Ar² are considered
15 distinguishable. As will be clear, however, the designation of one aromatic system as Ar¹ and the other as Ar² is arbitrary; thus there are only ten possible combinations. However, for simplicity, Ar¹ and Ar² are designated separately with the realization that the choice is arbitrarily made. All linkers described herein if not palindromic, are considered to link Ar¹ to Ar² or *vice-versa* whether or not the complementary
20 orientation is explicitly shown (as it is in some cases). Thus, if Ar¹ and Ar² are different and a linker is specified as -CONR-, it is understood that also included is the linker -NRCO- when the designations Ar¹ and Ar² are retained.

The noninterfering substituents on the aromatic system represented by Ar¹ and the noninterfering substituents on the aromatic system represented by Ar² are
25 represented in the formulas herein by R^a and R^b, respectively. Generally, these substituents can be of wide variety. Among substituents that do not interfere with (and in some instances may be desirable for) the beneficial effect of the compounds of the invention on bone in treated subjects are included alkyl (1-6C, preferably lower alkyl 1-4C), including straight or branched-chain forms thereof, alkenyl (1-6C, preferably 30 1-4C), alkynyl (1-6C, preferably 1-4C), all of which can be straight or branched chains

or are aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C) and may contain further substituents. R^a and R^b may also include halogens, (e.g. F, Cl, Br and I); siloxy, OR, SR, NR₂, OOCR, COOR, NCOR, NCOOR, and benzoyl, CF₃, OCF₃, SCF₃, N(CF₃)₂, NO, NO₂, CN, SO, SO₂R, SO₃R and the like, wherein R is alkyl (1-6C) or is H.

5 Similarly, these substituents may contain R' as a substitute for R wherein R' is aryl (6-10C) or alkylaryl (6-15C) or aryl alkyl (6-15C). Where R^a or R^b substituents are in adjacent positions in the aromatic system, they may combine to form a ring. Further, rings may be included in substituents which contain sufficient carbon and heteroatoms to provide this possibility.

10 The choice of noninterfering substituents depends on the overall nature of the system. For example, in compounds of the invention wherein two pyridine rings are linked through a saturated flexible linker, a CF₃ substituent para to the linker in each of the pyridine rings is particularly preferred. In those systems wherein a quinoline is coupled through a flexible conjugated or nonconjugated linker to a phenyl substituent or to a naphthyl substituent, an amino group para to the linker in the phenyl or naphthyl moiety is preferred. Particularly preferred amino groups are dimethylamino and diethylamino. In systems wherein a benzothiazole is coupled to phenyl through a flexible linker, preferred substituents on the phenyl moiety include alkoxy or alkylthio in combination with halo, in particular, chloro. Also preferred is the presence of a 15 diethylamino group in the phenyl moiety para to the position that is coupled to the linker. In general, the presence of a substituent in the phenyl moiety para to the position of joinder to the linker is preferred.

20 Generally, preferred noninterfering substituents include hydrocarbyl groups of 1-6C, including saturated and unsaturated, linear or branched hydrocarbyl as well as hydrocarbyl groups containing ring systems; halo groups, alkoxy, hydroxy, amino, monoalkyl- and dialkylamino where the alkyl groups are 1-6C, CN, CF₃, OCF₃, and COOR, and the like.

25 Although the number of R^a and R^b may typically be 0-4 (m) or 0-5 (n) depending on the available positions in the aromatic system, preferred embodiments

include those wherein the number of R^a is 0, 1 or 2 and of R^b is 0, 1, 2 or 3, particularly 1 or 2.

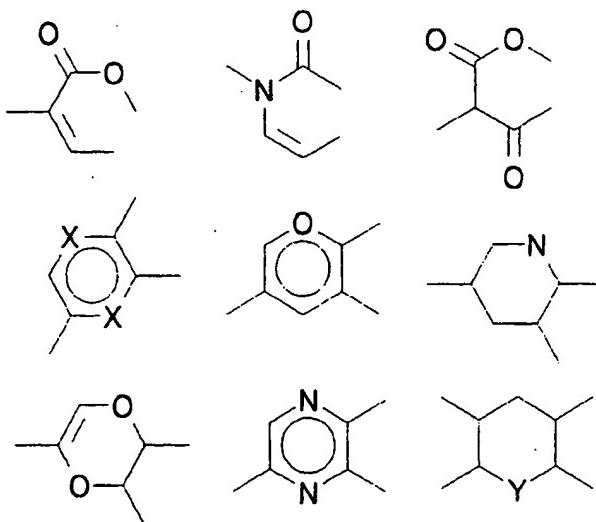
The linker group, L, may be a covalent bond or any group having a valence of at least two and covering a linear distance of from about 1.5 to about 15 Angstroms, 5 including those that contain cyclic moieties, that meet this spatial requirement. Useful linkers are divided, by definition herein, into three general categories: (1) flexible nonconjugating linkers, (2) flexible conjugating linkers, and (3) constrained linkers. The preferred choice of linker will depend on the choices for Ar¹ and Ar².

As defined herein, *flexible nonconjugating* linkers are those that link only one 10 position of Ar¹ to one position of Ar², and provide only a single covalent bond or a single chain between Ar¹ and Ar². The chain may contain branches, but may not contain π -bonds (except in the branches) or cyclic portions in the chain. The linker atoms in the chain itself rotate freely around single covalent bonds, and thus the linker has more than two degrees of freedom. Particularly useful flexible nonconjugating 15 linkers, besides a covalent bond, are those of the formulas: -NR-, -CR₂-, -S-, or -O-, wherein R is H or alkyl (1-6C), more preferably H or lower alkyl (1-4C) and more preferably H. Also contemplated are those of the formulas: -NRCO-, -CONR-, -CR₂S-, -SCR₂-, -OCR₂-, -CR₂O-, -NRNR-, -CR₂CR₂-, -NRSO₂-, -SO₂NR-, -CR₂CO-, -COCR₂-, and -NR-NR-CO-CR₂- and its complement -CR₂-CO-NR-NR-, 20 or -NRCR₂CR₂NR- or the thiolated counterparts, and particularly -NHCR₂CR₂NH-, including the isosteres thereof, such as -NRNRCSNR- and -NRNRCONR-. Also contemplated are those of the formulas: -NH(CH₂)₂NH-, -O(CR₂)₂O-, and -S(CR₂)₂S-, including the isosteres thereof. The optimum choice among flexible nonconjugating linkers is dependent on the nature of Ar¹ and Ar².

25 *Flexible conjugating* linkers are those that link only one position of Ar¹ to one position of Ar², but incorporate at least one double or triple bond or one or more cyclic systems in the chain itself and thus have only two degrees of freedom. A flexible conjugating linker may form a completely conjugated π -bond linking system between Ar¹ and Ar², thus providing for co-planarity of Ar¹ and Ar². Examples of useful 30 flexible conjugating linkers include: -RC=CR-; -N=N-; -C≡C-; -RC=N-; -N=CR-;

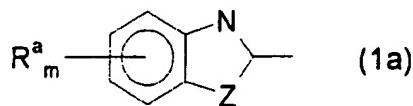
-NR-N=CR-, -NR-NR-CO-CR=CR-, -N=NCOCR₂-, -N=NCSCR₂-, -N=NCOCR₂CR₂, -N=NCONR-, -N=NCSNR-, and the like, where R is H or alkyl (1-6C); preferably H or lower alkyl (1-4C); and more preferably H.

- Constrained linkers* are those that have more than one point of attachment to either or both Ar¹ and Ar² and, thus, generally allow for only one degree of freedom. Constrained linkers most frequently form fused 5- or 6-membered cyclic moieties with Ar¹ and/or Ar² where either Ar¹ or Ar² has at least one substituent appropriately positioned to form a second covalent bond with the linker, e.g., where Ar² is a phenyl group with a reactive, ortho-positioned substituent, or is derivatized to the linker directly at the ortho position. (Although the aromatic moieties should properly be referred to as phenylene or naphthylene in such cases, generally the term "phenyl" or "naphthyl" is used herein to include both monovalent and bivalent forms of these moieties.) Examples of particularly useful constrained linkers include

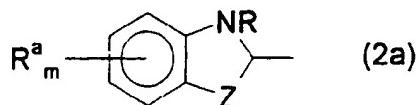


- 15 and the like, where X is O, N, S or CR, and Y is CR₂ or C=O.

In one class of preferred embodiments, Ar¹ is an aromatic system containing a 5-membered heterocycle, of the formula:



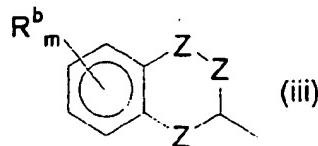
or



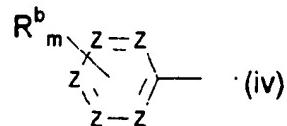
wherein Z is S, O, NR or -CR₂ in formula (1a) or CR in formula (2a), where each R is independently H or alkyl (1-6C), the dotted line represents an optional π -bond, each R^a is independently a noninterfering substituent as defined above, and m is an integer of 0-4.

In general, Ar² is phenyl, naphthyl, or an aromatic system containing a 5- or 6-membered heterocyclic ring. All may be unsubstituted or substituted with noninterfering substituents, R^b.

When Ar² is an aromatic system containing a six-membered heterocycle, the formula of said system is preferably:

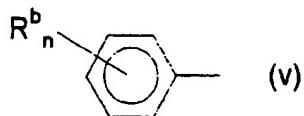


or



wherein each Z is independently a heteroatom selected from the group consisting of S, O and N; or is CR or CR₂, the dotted lines represent optional π -bonds, each R^b is independently a noninterfering substituent, and m is an integer of 0-4, with the proviso that at least one Z must be a heteroatom.

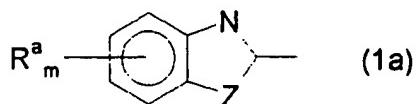
Ar² in these compounds may also have the formula



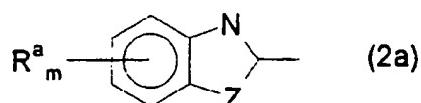
where R^b is a noninterfering substituent as defined above and n is an integer from 0 to 5.

Similarly, when Ar^2 is naphthyl, it may contain 0-5 R^b substitutions. When Ar^2 is an aromatic system containing a 5-membered heterocycle, preferred forms are those as described for Ar^1 .

Thus, in one set of preferred compounds, Ar^1 is

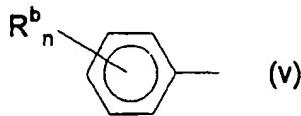


or



wherein each R^a is a noninterfering substituent, m is an integer of 0-4, the dotted line represents an optional π bond, and Z is O, S, NR or CR_2 in formula (1) or is CR in formula (2) wherein each R is independently H or alkyl (1-6C).

In one group of these compounds, L is a flexible conjugating or nonconjugating linker. In this group, when Z is NR, Ar^2 is preferably a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is



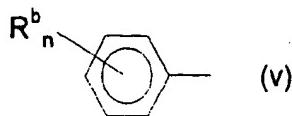
;

wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is $-N=N-$, $-N=CR-$, $-RC=CR-$, $-NRNR-$, $-CR_2NR-$, $-CR_2CR_2-$, $-NRCO-$ or $-CONR-$ where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

In these embodiments as well as in alternative embodiments of Ar², it is preferred that each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C), or R^b comprises an aromatic system.

Preferred compounds in this group are 59-0100, 59-103, 59-104, 59-105 and 5 59-106 (See Figure 13).

In another group of these compounds with flexible linkers, Z is S, and Ar² is preferably a substituted or unsubstituted aromatic system containing a 6-membered heterocycle or is of the formula



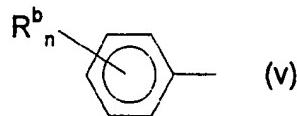
10 wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C); and/or the dotted line represents a π bond.

15 In such compounds, regardless of the choice of Ar², preferred are those compounds wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

Both when Z is S and when Z is NR, it is preferred that m is 0 and/or each R^b is independently OR, SR or halo, where n=2 and at least one R^b is independently OR or SR and/or L is -NHCO- or -CR=CR-.

Preferred compounds in this group include compounds 59-002, 59-0070, 20 59-0072, 59-0099, 59-0102, the benzothiazole counterpart of 59-0104, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195, 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210, especially the benzothiazole counterpart of 59-0104 or compounds 59-0147, 59-0205 or 59-0210. (See Figure 13)

25 Z can also be CR, CR₂ or O; here it is also preferred that Ar² is

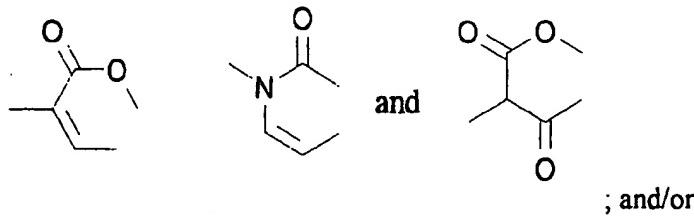


wherein R^b is a noninterfering substituent and n is an integer of 0-5, and/or L is
 $-N=N-$, $-N=CR-$, $-RC=CR-$, $-NRNR-$, $-CR_2NR-$, $-CR_2CR_2-$, $-NRCO-$ or $-CONR-$
 where R is H or alkyl (1-6C), and/or the dotted line represents a π bond.

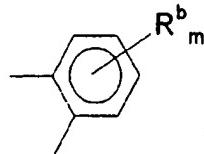
5 In these compounds, too, it is preferred that each R^b is independently halo, OR,
 SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an
 aromatic system. A preferred compound is 896-5005. (See Figure 4)

The compounds wherein Ar¹ is 1a or 2a as above may also contain a
 constrained linker.

10 In these compounds, preferred Z is S or NR; and/or those wherein L is selected
 from the group consisting of



Ar² is



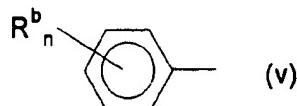
15 wherein R^b is a noninterfering substituent and m is 0-4.

Preferably, each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or
 CF₃, wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system. A preferred
 compound is 59-0124. (See Figure 13)

In another group of preferred embodiments, Ar¹ is of the formula

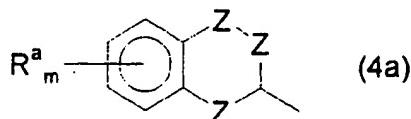


wherein each R^a is independently a noninterfering substituent or is H and Z is NR, S or O, wherein R is alkyl (1-6C) or H, especially where Z is S and/or wherein Ar^2 is



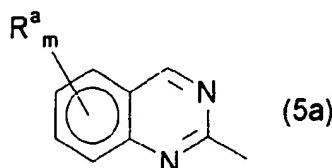
5 wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or -CONR- where R is H or alkyl (1-6C), and/or the dotted line represents a π bond. Especially preferred are those compounds where each R^b is independently halo, OR, SR, NR₂, 10 NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In another group of compounds, Ar^1 is

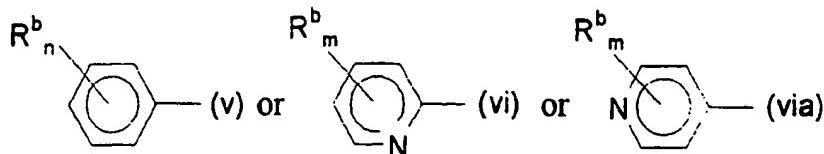


15 wherein R^a is a noninterfering substituent, m is an integer of 0-4, each dotted line represents an optional π -bond, each Z is independently N, NR, CR or CR₂, where each R is independently H or alkyl (1-6C) with the proviso that at least one Z is N or NR.

Particularly preferred members of this group are those wherein Ar^1 is



especially those wherein Ar₂ is

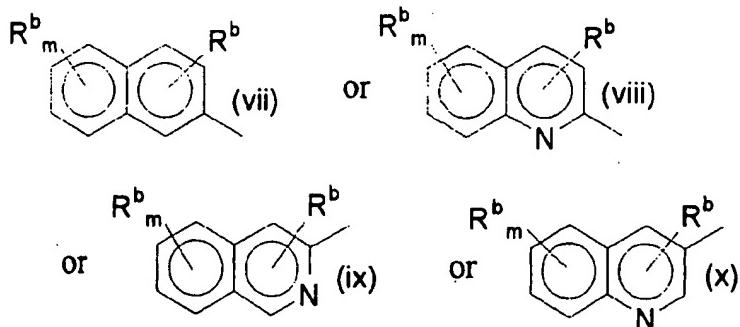


wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4, and/or L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCCR₂CR₂-, 5 -NRCCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCCR₂CR₂NR-, -NRCCR=CRNR- or -NRCOCCR₂NR-.

In general, preferably each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

In an especially preferred group, m is 0, each R^b is NR₂ or OR and n is 1 or 2, 10 and/or L is -CR=CR-, -N=N- or -NRCO-, especially the compounds of formulas 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or 59-0480. (See Figure 13)

Also preferred are those wherein Ar¹ has formula (4a) or (5a) and wherein Ar₂ is substituted or unsubstituted quinolyl or naphthyl of the formula



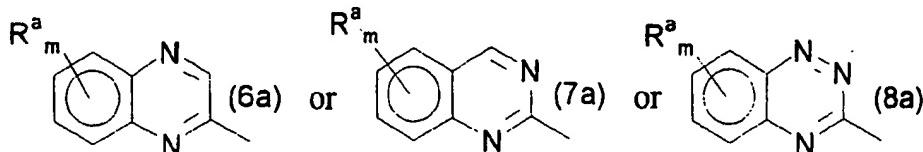
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wherein each R^b is a noninterfering substituent and m is 0-4.

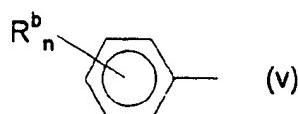
Preferred among these are those wherein L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCCR₂CR₂-, -NRCCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCCR₂CR₂NR-, -NRCCR=CRNR- or -NRCOCCR₂NR-, and/or wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.

The compounds 59-0089, 59-0090, 59-0092 or 59-0094 are particularly preferred.

Ar^1 is also preferably



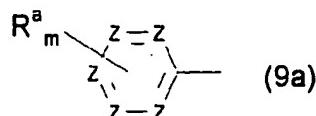
5 wherein each R^a is a noninterfering substituent and m is 0-4, in particular where L is $-\text{N}=\text{N}-$, $-\text{RC}=\text{CR}-$, $-\text{RC}=\text{N}-$, $-\text{NRCO}-$, $-\text{NRCR}_2-$, $-\text{NRCR}_2\text{CR}_2-$, $-\text{NRCR}_2\text{CO}-$, $-\text{NRNR}-$, $-\text{CR}_2\text{CR}_2-$, $-\text{NRCR}_2\text{CR}_2\text{NR}-$, $-\text{NRCR}=\text{CRNR}-$ or $-\text{NRCOCLR}_2\text{NR}-$, and/or Ar^2 is



10 wherein R^b is a noninterfering substituent and n is an integer of 0-5. Especially preferred are compounds wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system, in particular compounds 59-203, 59-285 or 59-286. (See Figure 13)

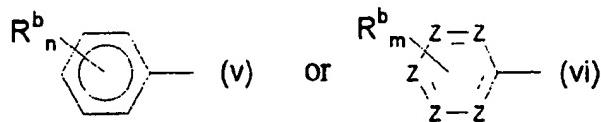
When Ar^1 is of formula (4a), L can also be a constrained linker.

15 In still another preferred set, Ar^1 is



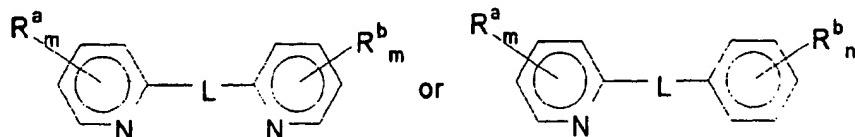
wherein each R^a is independently a noninterfering substituent, m is an integer of 0-4, each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be N and at least one Z must be CR.

20 In these compounds, L is preferably a flexible conjugating or nonconjugating linker, and/or wherein Ar^2 is



wherein each R^b is independently a noninterfering substituent, and in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

5 Preferred such compounds have the formula



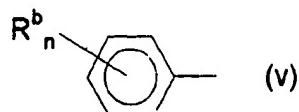
Preferred L embodiments in this group include -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NR₂CR₂-, -NR₂CR₂CO-, -NRNR-, -CR₂CR₂-, -NR₂CR₂CR₂NR-, -NR₂CR=CRNR- or -NRCOOCR₂NR-; preferred for R^a and R^b are halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^a or R^b comprise aromatic systems and each m and n is independently 0, 1 or 2.

In particular, compounds are preferred where L is -NHCR₂CR₂NH- and R^a is CF₃ para to L, especially compounds 59-0145, 59-0450, 59-0459 or 59-0483. (See Figure 13)

15 Finally, in another preferred group, Ar¹ is



wherein each R^a is a noninterfering substituent, and n is an integer of 0 and 5, and wherein L is a flexible linker that contains at least one nitrogen. In the alternative or in addition, Ar² is of the formula



- and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-,
-NRCR₂CO-, -NRNRCR₂CR₂-, -NRNRCR=CR-, -NRNRCOCR₂-,
-NRNRCOCR=CR-, -NRNRCSCR₂-, -NRNRCSCR=CR-, -NRNRCCONR-,
-NRNRCNSR-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or
5 -NRCOCR₂NR-. It is preferred that each R^b is independently halo, OR, SR, NR₂, NO,
NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.
Especially preferred are those compounds wherein L is -CR=CRCONRNR-,
-CR=CRCSNRNR-, -CR₂CONRNR- -CR₂CSNRNR-, -NRNRCONR- or
-NRNRCNSR- and/or R^b is -NR₂ and n=1 wherein R^b is in the para position, especially
10 wherein R^a is -COOR and m is 1; most especially compounds 59-0045, 59-0095,
59-0096, 59-0097 and 59-0098. (See Figure 13)
- As set forth above, several families of preferred embodiments are defined by specifying Ar¹ and Ar², and L. In one such family, wherein Ar¹ is an aromatic system containing a 5-membered heterocyclic ring, the compound 59-0072, wherein Ar¹ is
15 unsubstituted benzothiazole, the linker (Ar¹ → Ar²) is NHCO, and Ar² is 2-methoxy-4-methylthiophenyl was used as a lead compound and variations of the structure studied. Figure 5 shows representative compounds synthesized to analyze the effects of the nature of the linker, various alternatives of Ar¹ wherein Z is O, NR or S, and the effect of substitution on the phenyl moiety, as well as the heterocycle.
- 20 Figure 5 gives the structures of these compounds, along with their maximum activity as compared to 59-0008 at 10 μM (the maximum for 59-0008) in the *in vitro* bone growth stimulation assay as well as the concentration at which 50% of maximum stimulation of the BMP promoter was obtained (EC₅₀). See Example 1 for the details of this assay. The results of this study indicate that the amide linker in 59-0072 can
25 readily be substituted by -CH=CH- and that the substitution on the phenyl ring had advantageous effects in the order: 2-Cl-4-OMe=2,4-di-OMe=2-OMe-4-SMe
>>3,4-di-OMe=4-OMe. In general, compounds 59-0205, 59-0104, 59-0107, 59-0210 and 59-0124 have the best activity in the primary screen, but only 59-0124 is active in the *ex vivo* calvarial assay described in Example 3.

Similar structure/activity relationship studies were conducted for compounds wherein Ar¹ is quinoline. In this study, compound 50-0197, wherein Ar¹ is unsubstituted quinoline, the linker is -CH=CH-, and Ar² is p-dimethylaminophenyl was used as a lead compound. The compounds synthesized in this study are shown in

- 5 Figure 6, along with their maximum stimulation characteristics and EC₅₀ in the assay of Example 1. The results of these studies showed that quinoxaline analogs are the most active in the assay, followed by quinoline; the linker can most preferably be -CH=CH- or -N=N- as judged by activity in the assay, but -CH=CH- is preferred *in vivo* due to its lack of toxicity. Preferred substituents on the phenyl ring in Ar² include 2,4-di-
10 OMe; 4-NMe₂-2-OMe, and 4-NMe₂. For the compounds in Figure 6, 59-0282 and 50-0197 were moderately active and 59-0203 was highly active in the *ex vivo* calvarial assay described hereinabove as a modification of Gowen, M. and Mundy, G. *J Immunol* (1986) 136:2478-2482.

Another group of compounds wherein Ar¹ and Ar² are pyridyl heterocycles was
15 also studied. In this case, compound 59-0145 was used as the lead compound; the linker, the nature of the substituents R^a and R^b were varied. In one instance, a quinolyl residue was substituted for a pyrimidine residue as Ar². Representative compounds used in this study are shown in Figure 7, along with the data from the screening assay.

Using 59-0145 as a lead, a CF₃ group in one of Ar¹ and Ar² appeared essential;
20 however, one of R^a or R^b could also be NO₂ or CN. The most preferred linker is -NHCH₂CH₂NH-; substitution on the amino groups in L by an alkyl group appeared to reduce activity. Enhanced chain lengths also led to loss of activity.

Preferred compounds in this group, which perform better than 59-0008 in the screening assay, included 59-0450, 59-0459, 59-0480, and 59-0483.

- 25 Finally, a series in which Ar¹ is 3-carboxyphenyl was studied using 59-0045 as the lead compound. In 59-0045, L is -NHN=CH- and Ar² is p-dimethylaminophenyl. Figure 8 shows the compounds synthesized in this series. Under the circumstances of this assay, analogs wherein R^b was, instead of a nitrogen-containing moiety, F, Cl, or OMe were inactive. Preferred compounds in this series are 59-0096 and 59-0098.
30 59-0098 is very active in the *ex vivo* calvarial assay described above.

Synthesis of the Compounds Useful in the Invention

Many of the compounds useful in the invention are commercially available and can be synthesized by art-known methods. Those compounds useful in the invention which are new compounds, can similarly be obtained by methods generally known in the art, as described in the Examples below.

The following examples are intended to illustrate, but not to limit, the invention.

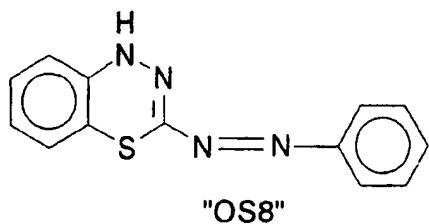
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Preparation A

Compound 59-0008 used as a standard in the assays, was synthesized according to the procedure of McDonald, W. S., *et al. Chem Comm* (1969) 392-393; Irving, H. N. N. H. *et al. Anal Chim Acta* (1970) 49:261-266. Briefly, 10.0 g of dithizone was taken up in 100 ml EtOH and 50 ml AcOH and heated at reflux for 18 h. After cooling, this was diluted first with 100 ml water and then with 50 ml 1N NaOH. This was then further neutralized by the addition of 6 N NaOH to bring the pH to 5.0. This deep purple mixture was then concentrated on a rotavapor to remove organics. Once the liquid had lost all of its purple color, this was filtered to collect the dark precipitate. Purification by flash chromatography (4.5 x 25.7 cm; EtAc/Hep. (1:4); Rf 0.22) followed by recrystallization from EtOH gave 2.15 g (25% yield) of dark purple crystals, mp=184-185 °C. ¹H NMR (CDCl₃) 7.90 (d of d, J₁=7.7, J₂=2.2, 2H), 7.64 (hump, 1H), 7.49 (m, 3H), 7.02 (m, 1H), 6.91 (m, 2H), 6.55 (d, J=8.1, 1H). MS (EI) 254 (47, M⁺), 105 (26), 77 [100], 51 (27). HRMS (EI, M⁺) 254.0626 (calcd 254.0626182). Anal. Calcd for C₁₃H₁₀N₄S: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.40; H, 4.20; N, 22.06.

Example 1High Throughput Screening

Several tens of thousands of compounds were tested in the assay system set forth in WO 96/38590, published 5 December 1996, and incorporated herein by reference. The standard positive control was 59-0008 (also denoted "OS8"), which is 5 of the formula:



In more detail, the 2T3-BMP-2-LUC cells, a stably transformed osteoblast cell line described in Ghosh-Choudhury *et al.* *Endocrinology* (1996) 137:331-39, 10 referenced above, was employed. The cells were cultured using α -MEM, 10% FCS with 1% penicillin/streptomycin and 1% glutamine ("plating medium"), and were split 1:5 once per week. For the assay, the cells were resuspended in a plating medium containing 4% FCS, plated in microtiter plates at a concentration of 5×10^3 cells (in 50 μ l)/well, and incubated for 24 hours at 37°C in 5% CO₂. To initiate the assay, 50 μ l of 15 the test compound or the control in DMSO was added at 2X concentration to each well, so that the final volume was 100 μ l. The final serum concentration was 2% FCS, and the final DMSO concentration was 1%. Compound 59-0008 (10 μ M) was used as a positive control.

The treated cells were incubated for 24 hours at 37°C and 5% CO₂. The 20 medium was then removed, and the cells were rinsed three times with PBS. After removal of excess PBS, 25 μ l of 1X cell culture lysing reagent (Promega #E153A) was added to each well and incubated for at least ten minutes. Optionally, the plates/samples could be frozen at this point. To each well was added 50 μ l of 25 luciferase substrate (Promega #E152A; 10 ml Promega luciferase assay buffer per 7 mg Promega luciferase assay substrate). Luminescence was measured on an

automated 96-well luminometer, and was expressed as either picograms of luciferase activity per well or as picograms of luciferase activity per microgram of protein.

In this assay, compound 59-0008 (3-phenylazo-1H-4,1,2-benzothiadiazine) exhibited a pattern of reactivity, as shown in Figure 2. The activity for compound 5 59-0008 was maximal at a concentration of approximately 3-10 μ M and, more particularly, at about 3 μ M, and thus provided a response of approximately 175 light emission units. Accordingly, other tested compounds were evaluated at various concentrations, and these results were compared to the results obtained for 59-0008 at 10 μ M (which value was normalized to 100). For instance, any tested compound in 10 Figure 3 and Figure 4 that showed greater activity than 10 μ M of 59-0008 would result in a value over 100.

As shown in Figure 3 (46 sheets) and Figure 4 (28 sheets), several compounds were found to be particularly effective.

15

Example 2

In vivo Calvarial Bone Growth Data

Compound 59-0008 was assayed *in vivo* according to the procedure described previously (see "In vivo Assay of Effects of Compounds on Murine Calvarial Bone Growth", *supra*). As compared to a vehicle control, compound 59-0008 induced a 4- 20 fold increase in width of new calvarial bone.

In another experiment, 5 week old Swiss white mice were injected 3 times a day for 5 days over the calvaria with compound 59-0203 using PBS, 5% DMSO and 0.1% BSA as carrier. The drug was tested at 6 different doses, from 0.1-50 mg/kg/day. Animals were sacrificed 3 weeks after the injections started and calvariae 25 were fixed, decalcified, and processed for histology. Bone histomorphometry measuring total bone area (BA/TV) confirms that FGF, used in every experiment as a positive control, shows an increase in the total bone area with all doses tested, but this increase is only significantly different from control at 1 and 5 mg/kg/day. The invention compound 59-0203 shows consistent increases over the 0.1-50 mg/kg/day 30 range at a somewhat lower level than that obtained with FGF.

Similar results are obtained when new bone width in microns is measured.

There was no new bone present in the control group. 59-0203 caused new bone formation at all doses, with a significant increase at 25-50 mg/kg/day. New bone as percentage of the total bone area was about 45% for the FGF positive control and 5 from about 15% to 30% over the range of 0.1-50 mg/kg/day for 59-0203. There was no new bone present in the negative control.

Example 3

Ex vivo Calvarial Bone Growth Assay

- 10 A number of compounds, in particular, those studied in connection with lead compounds classified as hydrazone/hydrazides (H) exemplified by 59-0045, benzothiazoles (T) exemplified by 59-0104, bis-pyridines (P) exemplified by 59-0145, and quinolines/quinoxalines (Q) exemplified by 59-0197, were tested in the *ex vivo* calvarial assay described hereinabove. The results of this assay are shown in Figure 9.
- 15 In this assay, histomorphometry and osteoblast numbers are measured and effects are measured on an arbitrary scale from 1-3: i.e., 1, 1+, 2-, 2, 2+, 3-, 3, wherein 1 denotes "inactive." In this assay, for example, FGF scores 2-3.

The scores are assigned to bone formation on the ectocranial periosteal surface.

The area immediately surrounding midline suture is excluded from analysis.

20

Score

- 0 Toxicity. Cell necrosis, pyknotic nuclei, matrix disintegration.
- 25 1 A score of "1" is the bone forming activity seen in control cultures containing BGJb media + 0.1% bovine serum albumin. The periosteal surface is covered by one layer of osteoblasts (at about 50% of the bone surface, with the remaining 50% being covered by bone lining cells). A score of "1-" is assigned if less than 50% of the periosteal surface is covered by osteoblasts due to inhibitory activity or minor toxicity of the agents being tested. A score of "1+" is given if over 50% of the surface is covered by osteoblasts.
- 30 2 A moderate increase in bone forming activity. 20-40% of the periosteal surface is covered by up to two layers of osteoblasts. A score of "2-" is given if less than 20% of the surface is covered by
- 35

two layers and "2+" if more than 40% of the surface is covered by two layers of osteoblasts.

- 5 3 A score of "3" is the bone forming activity seen in control cultures containing BGJb media + 0.1% BSA +10% fetal bovine serum. More than 20% of the periosteal surface is covered by three layers of osteoblasts. The cells appear plump (size can exceed 100 μm^2). A score of "3-" is given if less than 20% of the periosteal surface is covered by three layers of osteoblasts and or osteoblast size is less than 100 μm^2 . A score of "3+" has never been observed.
- 10

In all samples, toxicity, ectopic new or woven bone formation associated with osteoblasts, and osteoblast size as reflections of relative activity are noted.

- 15 The results shown in Figure 9 represent those obtained when the measurements were made by two different groups. It is clear that a number of compounds tested have activity in this assay. From the results shown in Figure 9, 59-0073, 59-0030, 59-0070, 59-007, 59-0019, 59-0099, 59-0072 and 59-0103 show at least some indication of activity. 59-150 and 59-0104 showed activity when measured by one group but not the other; similarly, 50-0197 had this pattern. It appears that 59-0098 and 59-0203 are quite active in this assay and 59-0145 shows a consistent moderate activity.
- 20

Example 4

Stimulation of Bone Growth in Ovariectomized Rats (OVX Assay)

- 25 The compound 59-0145 was tested at various concentrations in the OVX assay conducted as described above. The increase in bone volume was measured by two different groups; one group found 5 $\mu\text{g}/\text{kg}/\text{day}$ of 59-0145 gave 21% increase over control whereas the second group found a 71% increase. At 50 $\mu\text{g}/\text{kg}/\text{day}$, the first group found a 31% increase, and the second a 54% increase.

- 30 In another experiment, the lumbar vertebrae were measured and the above dosages of 59-0145 were shown to provide a beneficial effect, as shown in Figure 10.

In another experiment, 3 month old Sprague Dawley rats were ovariectomized and depleted for six weeks. At the end of the six weeks, treatment was started with subcutaneous administration of compound 59-0145. The treatment continued for 10

weeks. At the end of the 10 weeks animals were sacrificed, bones were collected for qCT measurements and histology; serum was also collected for osteocalcin determinations.

Figure 11 shows the percentage increase in trabecular bone (proximal tibia) compared to the placebo-treated group in chronic ovariectomized rats after 10 weeks of treatment. Compound 59-0145 causes significant increase in trabecular bone at doses of 50-500 µg/kg/day.

Figure 12 shows results of qCT and bone histomorphometry in proximal tibia in the first two panels, as well as serum osteocalcin levels at the time of sacrifice as a percentage increase compared to control group (OVX placebo-treated group).

Example 5

Chondrogenic Activity

Compounds 59-008, 59-0102 and 50-0197 were assayed for effects on the differentiation of cartilage cells, as compared to the action of recombinant human BMP-2. Briefly, a mouse clonal chondrogenic cell line, TMC-23, was isolated and cloned from costal cartilage of transgenic mice containing the BMP-2 gene control region driving SV-40 large T-antigen, generated as described in Ghosh-Choudhury *et al.* *Endocrinology* 137:331-39, 1996. These cells were cultured in DMEM/10% FCS, and were shown to express T-antigen, and also to produce aggrecan (toluidine blue staining at pH 1.0) and Type-II collagen (immunostaining) by 7 days after confluence.

For measurement of alkaline phosphatase (ALP) activity, the technique of LF Bonewald *et al.* *J Biol Chem* (1992) 267:8943-49, was employed. Briefly, TMC-23 cells were plated in 96 well microtiter plates in DMEM containing 10% FCS at 4 x 10³ cells/well. Two days after plating, the cells were confluent and the medium was replaced with fresh medium containing 10% FCS and different concentrations of compounds or recombinant BMP-2. After an additional 2 or 5 days incubation, the plates were washed twice with PBS, and then lysing solution (0.05% Triton X-100) was added (100 µl/well). The cells were lysed by three freeze-thaw cycles of -70°C (30 min), followed by 37°C (30 min with shaking). Twenty microliters of cell lysates

were assayed with 80 µl of 5 mM p-nitrophenol phosphate in 1.5 M 2-amino-2-methyl-propanol buffer, pH 10.3 (Sigma ALP kit, Sigma Chemical Co., St. Louis, MO) for 10 min at 37°C. The reaction was stopped by the addition of 100 µl of 0.5 M NaOH. The spectrophotometric absorbance at 405 nm was compared to that of p-nitrophenol standards to estimate ALP activity in the samples. The protein content of the cell lysates was determined by the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA). Specific activity was calculated using these two parameters.

At day 2, compounds 59-0008 (10^{-9} M), 59-0102 (10^{-7} M) and 59-0197 (10^{-9} M) increased ALP levels approximately 3-, 2- and 2.5-fold, respectively, as compared to the vehicle control. Recombinant BMP2 at 100, 50 or 10 ng/ml induced ALP levels approximately 10-, 4- or 1.5-fold, respectively, as compared to the vehicle control.

Example 6

Synthesis of Exemplary Compounds

A. Compounds of the invention wherein Ar¹ is of formula (1a) or (2a) can be synthesized by the procedures described in Dryanska, V. and Ivanov, K. *Synthesis* (1976) 1:37-8, using the described embodiments of Ar² and the appropriate analogous heterocycle embodied in Ar¹ substituted for the benzothiazole shown. Alternates to the olefin linker described can also be prepared using standard methods.

Compounds of the invention represented by exemplary Compound 59-0234, wherein Z is O, L is -CH=CH-, and Ar² is 2,4-dimethoxy-phenyl, including Compounds 59-0211 and 59-0233, were prepared according to the following procedure describing synthesis of Compound 59-0234. Briefly, to a N,N-dimethylformamide (DMF) solution of 2-methylbenzoxazole (1 mmol) and 2,4-dimethoxybenzaldehyde (1 mmol) was added lithium t-butoxide (2 mmol). The reaction mixture was heated at 130°C for 3h. After cooling to room temperature, the reaction mix was poured into ether and washed several times with water. The organic phase was dried over Na₂SO₄, filtered, and evaporated to dryness. The residue was dissolved in a minimal amount of hot ether and, on standing overnight, the crystalline product was collected by filtration.

B. Exemplary Compound 59-0150 where Ar¹ is of formula 4a was synthesized according to the procedure of Zamboni *et al. J Med Chem* (1992) 35:3832-44. First, 2-triphenylphosphoniumquinaldine bromide was synthesized as follows. Quinaldine (200 mmols), NBS (200 mmols) and a catalytic amount of 5 benzoyl peroxide (10 mmols) were dissolved in 1 L of anhydrous carbon tetrachloride, and the mixture was stirred under reflux for 72 h. The mixture was cooled to RT and washed with water. The organic layer was drawn off, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a dark oil. The crude mixture was dissolved in 500 ml of acetonitrile, then triphenylphosphine (200 mmols) was added 10 and the mixture was refluxed under nitrogen overnight. It was then cooled to RT and diluted with anhydrous ether. The precipitated solid was collected by filtration, washed thoroughly with anhydrous ether and dried in vacuo overnight, yielding 25 g of a tan crystalline solid which showed a single spot by TLC (silica gel, 5 % MeOH in DCM).

15 A Wittig reaction was then performed. Briefly, under anhydrous conditions, 0.738 g (1.68 mmol) 2-triphenylphosphoniumquinaldine bromide in dry THF was cooled to -78°C. 1.0 ml (2.5 mmol, 2.5 M in hexanes) n-butyl lithium was slowly added, and this was allowed to react for 20 min. 0.301 g (1.68 mmol) 4-(N,N-dimethylamino)-2-methoxybenzaldehyde was then added. After a few minutes, the 20 cold bath was removed, and this was left at ambient temp. for 18 h. The reaction was quenched by the addition of aq. sat. NH₄Cl. This was extracted with EtAc, and the organics washed with additional NH₄Cl, sat. NaHCO₃, and sat. NaCl. This was dried over anhydrous Na₂SO₄ and the solvent stripped on a rotavapor. After flash chromatography (3.8 x 18.0 cm; EtAc/Hep. (1:3); R_f 0.29), 0.135 g (26% yield) of a 25 red solid was obtained, mp=185-187 °C. ¹H NMR (CDCl₃) 8.04 (t, J=9.0, 2H), 7.94 (d, J=16.5, 1H), 7.74 (d, J=8.1, 1H), 7.73 (d, J=8.5, 1H), 7.66 (t of d, J_t=7.6, J_d=1.4, 1H), 7.61 (d, J=8.8, 1H), 7.43 (t of d, J_t=7.6, J_d=1.1, 1H), 7.29 (d, J=16.6, 1H), 6.37 (d of d, J₁=8.7, J₂=2.4, 1H), 6.22 (d, J=2.4, 1H), 3.93 (s, 3H), 3.03 (s, 6H).. Anal. Calcd for C₂₀H₂₀N₂O: C, 78.92; H, 6.62; N, 9.20. Found:

C. Exemplary Compound 59-0209 was synthesized according to the procedure of McOmie, J. F. W.; and West, D. E., *Org Synth, Collect Vol V* (1973)

412. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr₃ in dry CH₂Cl₂ at -78°C. After 15 min, this was

5 allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 ml MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped.

Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R_f 0.25) gave

10 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). ¹H NMR (DMSO-d₆) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C₁₇H₁₃NO: C, 82.57; H, 5.30; N, 5.66. Found:

15 D. Exemplary Compound 59-0019 was synthesized as follows: to a xylene solution of 2-methylquinoxaline (10 mmol) and 4-dimethylaminobenzaldehyde (10 mmol) was added piperidine (2 ml). The solution was heated at reflux for 1 day, at which time DBU (200 µL) was added and reflux continued for another 2 days. The solution was cooled to RT and extracted with 1 M citric acid. The aqueous phase was 20 repeatedly extracted with ether. The organic phases were pooled, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was chromatographed on silica gel. The product was eluted using 8:1:1 dicholormethane:ether: hexane. Fractions containing pure product were pooled and evaporated to dryness. The residue was triturated with ether and filtered to give the desired compound.

25 E. Exemplary Compound 59-0183 and related Compound 59-0182 were synthesized according to the following procedure. Briefly, quinaldic acid (0.5 mmol) and HATU (0.5 mmol) were dissolved in 2.5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (1 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min.

30 The appropriate amine (0.5 mmol) was then added all at once to the above stirred

mixture, and the mixture was stirred overnight at RT. It was then diluted with 25 mL of cold water with vigorous stirring, the precipitate was collected by filtration and washed thoroughly with water several times, and then dried *in vacuo* overnight. The product was purified by flash column chromatography over silica gel eluting with dichloromethane. The pure product was obtained as a tan powder.

F. Exemplary Compound 59-0209 was synthesized according to the following procedure. Under anhydrous conditions, 0.510 g (1.95 mmol) NNC 59-0198 was slowly treated with 0.38 ml (3.9 mmol) BBr₃ in dry CH₂Cl₂ at -78°C. After 15 min, this was allowed to warm to RT. After 2 h, the reaction was re-cooled to -78°C, and was then quenched by the addition of 1.6 ml (12 mmol) TEA in 25 mL MeOH. After 10 min, this was again allowed to warm to ambient temperature. After 1 h, this was concentrated to dryness on a rotavapor, and twice slurred in MeOH and re-stripped. Purification by flash chromatography (3.0 x 25.6 cm; EtAc/Hep. (1:2); R_f 0.25) gave 0.20 g (41% yield) of a slightly yellow solid, mp=271-272 °C (dec.). ¹H NMR (DMSO-d₆) 9.77 (s, 1H), 8.31 (d, J=8.6, 1H), 7.96 (d, J=8.6, 1H), 7.92 (d, J=8.3, 1H), 7.82 (d, J=8.6, 1H), 7.74 (d, J=16.6, 1H), 7.72 (t, J=7.6, 1H), 7.58 (d, J=8.6, 2H), 7.53 (t, J=7.6, 1H), 7.26 (d, J=16.5, 1H), 6.83 (d, J=8.6, 2H). Anal. Calcd for C₁₇H₁₃NO: C, 82.57; H, 5.30; N, 5.66. Found:

G. Other embodiments wherein AR¹ is of formula (4a) can be synthesized as follows:

a. Quinoline azo compounds (59-0030 and 59-0078) may be prepared by reaction of 2-aminoquinoline with a nitrosobenzene (Brown, E. V., *et al.*, *J Org Chem* (1961) 26:2831-33; Brown, E. V.; _____ (1969) 6:571-73).

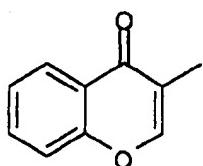
b. Azo derivatives may be obtained by reaction of 2-aminoquinolines with aldehydes, Morimoto, T., *et al.*, *Chem Pharm Bull* (1977) 25:1607-09; Renault, J., *et al.*, *Hebd Seances Acad Sci, Ser C* (1975) 280:1041-43; and Lugovkin, B. P.; *Zh Obshch Khim* (1972) 42:966-69.

c. Imino derivatives may be obtained by reaction of 2-formylquinolines with anilines, Tran Quoc Son, *et al.*, (1983) 21:22-26; Hagen,

V. et al. *Pharmazie* (1983) 38:437-39; and Gershuns, A. L., et al., *Tr Kom Anal Khim, Akad Nauk SSSR* (1969) 17:242-50.

d. Alternatively conjugated linkers can be formed by bromination of the olefin of 50-0197 with Br₂ in AcOH followed by elimination with DBU as set forth in Zamboni et al. *J Med Chem* (1992) 35:3832-44.

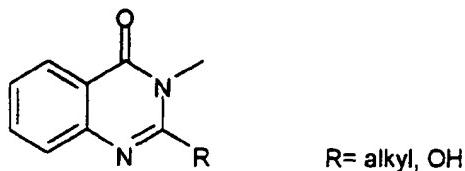
H. Analogs having the constrained linker depicted below:



may be synthesized by reference to the methods described in Gorbulenko, N.V.

10 et al. *Dokl Akad Nauk Ukr SSR* (1991) 5:117-23, substituting the 6-membered heterocycle for benzothiazole.

Related, compounds having the constrained linker depicted below:



15 may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87; Garin, J. et al. *Synthesis* (1984) 6:520-22, and Ayyangar N. R. et al. *Dyes and Pigments* (1990)

20 13:301-10.

I. Exemplary Compound 59-0145 can be synthesized according to the following method. Briefly, a mixture of 2-chloro-5-trifluoromethylpyridine (15 mmol), ethylenediamine (6 mmol), and diisopropylethylamine (18 mmol) was heated at reflux for 18 h. After cooling to room temperature, the solid mass was triturated with

dichloromethane. The product was filtered and then suspended in hot EtOAc:CHCl₃ (50:50, 800 mL) and filtered to remove insoluble material. The volume was reduced to ~200 mL by heating on a steam bath. On standing, crystals of pure product were deposited.

- 5 Related compounds may be synthesized by reference to the method described for Compound 59-0145, and by reference to the methods described in the following publications: Tzikas, A. & Carisch, C., US Patent No. 5,393,306, issued February 28, 1995; Herzig, P. & Andreoli, A., EP 580554, published January 26, 1994; Pohlke, R. & Fischer, W., DE 3938561, published May 23, 1991. Analogs containing the structure
10 O-(CH₂)_n-O may be synthesized by reference to the previous citations, as well as the following publications: Kawato, T. & Newkome, G. *Heterocycles* (1990) 31:1097-104; Kameko, C. & Momose, Y. *Synthesis* (1982) 6:465-66; Tomlin, C.D.S. *et al.*, GB 1161492, published August 13, 1969.

J. Exemplary Compound 59-0097 and exemplary Compound 59-0201
15 were synthesized according to the following general procedure. Briefly, the isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethylamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was
20 then diluted with 50 mL of cold water with vigorous stirring. The precipitate was collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder. The compounds of the invention are produced by
25 substituting for at least one phenyl group the appropriate heterocycle.

K. Compounds of the class represented by exemplary Compound 59-0045 can be synthesized using standard procedures for the synthesis of phenyl hydrazones of aromatic aldehydes, as described in any organic textbook. The synthesis of exemplary Compound 59-0045 may be performed as follows. Briefly, a suspension of 3-hydrazinobenzoic acid (1 mmol), p-dimethylaminobenzaldehyde (1 mmol), and AcOH
30

(50 μ L) in EtOH:H₂O (4 mL:1 mL) was heated at 105°C in a sealed vial for 3 h. After cooling, a bright yellow solid was removed by filtration. The solid was washed with cold MeOH and then with ether to give pure product.

L. Exemplary Compound 59-0096 and related, exemplary Compounds 59-0098, 59-0095, 59-0107, 59-0108, 59-0109, 59-0110 and 59-0200 may be synthesized according to the following general procedure. Briefly, the appropriate carboxylic acid (1 mmol) and HATU ([O-(7-azabenzotriazol-1-yl)-1,1,3,3-tritetramethyluronium hexafluorophosphate]; 1 mmol) were dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (3 mmol) was added dropwise to the above stirred solution and the mixture was stirred for 15 min. 3-Hydrazinobenzoic acid (1 mmol) was then added all at once to the above stirred mixture and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring and the precipitate was collected by filtration and washed thoroughly with water several times and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 - 10 % methanol in dichloromethane. The pure product was obtained as a tan crystalline solid.

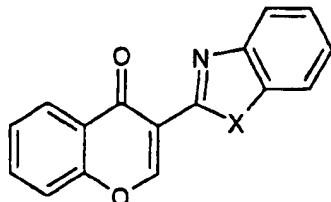
M. Exemplary Compound 59-0097 and exemplary Compound 59-0201 were synthesized according to the following general procedure. Briefly, the 20 isothiocyanate or isocyanate (1 mmol) was dissolved in 5 mL of anhydrous DMF in a vial and the solution was stirred at room temperature (RT). Diisopropylethyamine (2 mmol) was added dropwise to the above stirred solution followed by 3-hydrazinobenzoic acid (1 mmol), and the mixture was stirred overnight at RT. It was then diluted with 50 mL of cold water with vigorous stirring. The precipitate was 25 collected by filtration, washed thoroughly with water several times, and then dried in vacuo overnight. The product was purified by flash column chromatography over silica gel eluting with 5 % methanol in dichloromethane. The pure product was obtained as a red to purple powder.

N. Exemplary Compound 59-0125 where R¹ is methoxy, m is 1, the linker 30 is azo and Ar² is di(2-hydroxyethyl) amino, and related compounds having an azo

linker can be prepared in a manner similar to that described by Alberti, G. *et al. Chim Ind (Milan)* (1974) 56:495-97.

O. Exemplary Compound 59-0124 and related, constrained analogs having the structure depicted below:

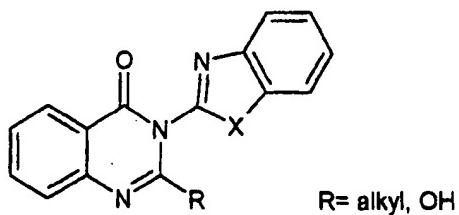
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may be synthesized by reference to the methods described in Gorbuleenko, N.V. *et al. Dokl Akad Nauk Ukr SSR* (1991) 5:117-23.

Related, constrained analogs having the structure depicted below:

10



R= alkyl, OH

may be synthesized by reference to the methods described in the following publications: Chaurasia, M.R. & Sharma, A.J. *Acta Cienc Indica Chem* (1992) 18:419-22; Kandeel, Maymona M., in *Phosphorus, Sulfur, Silicon, Relat Elem* (1990) 48:149-55; Salem, M.A. & Soliman, E.A. *Egypt J Chem* (1985) 27:779-87; Garin, J. *et al. Synthesis* (1984) 6:520-22, or according to the representative procedure described in Ayyangar N. R. *et al. Dyes and Pigments* (1990) 13:301-10.

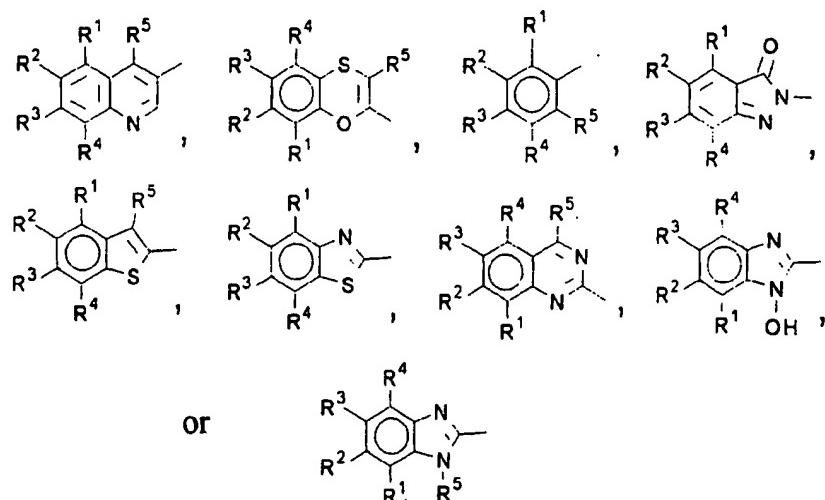
Claims

1. A method to treat a condition in a vertebrate animal characterized by a deficiency in, or need for, bone growth or replacement and/or an undesirable level of
 5 bone resorption, which method comprises administering to a vertebrate subject in need of such treatment an effective amount of a compound of the formula:

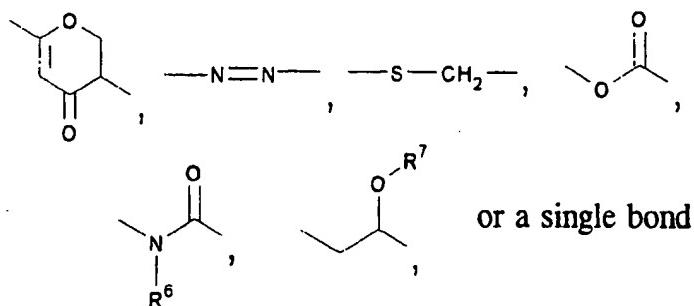


wherein each of Ar^1 and Ar^2 is independently a substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted aromatic system containing a 6-membered heterocycle or a substituted or unsubstituted aromatic system containing a 5-membered heterocycle; and
 10 L is a linker which spaces Ar^1 from Ar^2 at a distance of $1.5\text{\AA}-15\text{\AA}$.

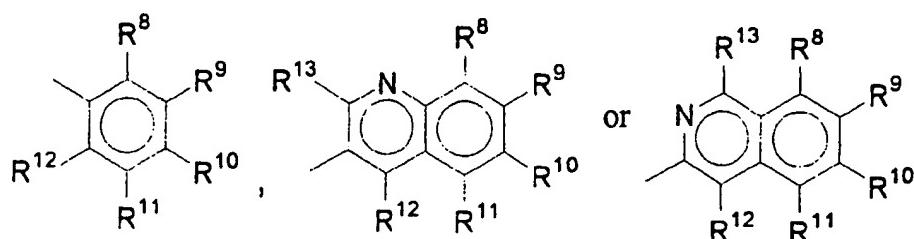
2. The method of claim 1 with the proviso that in the compound of
 15 formula (1), if Ar^1 is



and L is



Ar^2 cannot be



wherein

- 5 R¹ is selected from the group consisting of:
H, OH, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylthio, halo and (C1-C12)alkyl-carbonyloxy;

10 R² is selected from the group consisting of:
H, OH, halo, C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

15 R³ is selected from the group consisting of:
H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkenyl and (C1-C12)alkyl-carbonyloxy;

20 R⁴ is selected from the group consisting of:
H, OH, halo, C1-C6 alkyl, C1-C6 alkoxy and (C1-C12)alkyl-carbonyloxy;

 R⁵ is selected from the group consisting of:
H, halo, C1-C6 alkyl, C1-C6 alkoxy, -OC(=O)Me, phthalimide and (C1-C12)alkyl-carbonyloxy;

 R⁶ is selected from the group consisting of:
H, OH, -NH₂, Cl-C4 alkyl and C1-C4 alkoxy;

R^7 is selected from the group consisting of:

H, C1-C4 alkyl, (C1-C4)alkyl-carbonyl and (C7-C10)arylalkyl;

R^8 is selected from the group consisting of:

H, OH, halo, -CF₃, C1-C4 haloalkyl, C1-C4 alkyl, C1-C4 alkoxy,

5 -NHC(=O)Me and -N(C1-C4 alkyl)₂;

R^9 is selected from the group consisting of:

H, OH, halo, -CN, -NO₂, C1-C4 haloalkyl, C1-C8 alkyl, C1-C8 alkoxy,

-NHC(=O)Me and -OC(=O)Me;

R^{10} is selected from the group consisting of:

10 H, OH, halo, -CN, -NO₂, C1-C4 haloalkyl, -CO₂H, C1-C12 alkyl, C1-C12 alkoxy, phenyl, C1-C12 alkenyl, (C1-C4)alkoxycarbonyl, -NHC(=O)Me, (C1-C4)alkylcarbonyl, (C1-C12)alkylcarbonyloxy and heteroaryl;

R^{11} is selected from the group consisting of:

H, OH, halo, C1-C4 haloalkyl, -CF₃, C1-C4 alkyl, -NH₂, C1-C4 alkoxy,

15 -NHC(=O)Me, C1-C4 alkenyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, and (C1-C4)alkylcarbonyloxy;

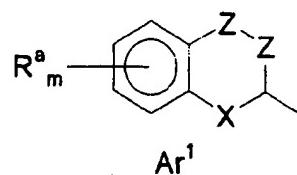
R^{12} is selected from the group consisting of:

H, OH, -NH₂, C1-C4 alkyl, C1-C4 alkoxy and (C1-C4)alkylcarbonyl; and

R^{13} is selected from the group consisting of:

20 H, OH, halo, -NH₂, C1-C4 alkyl, C1-C4 alkoxy -N(C1-C4)alkyl.

3. The method of claim 1 with the proviso that in the compound of formula (1), if Ar¹ is



25 wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π-bond;

each Z is independently N, NR, O, S, CR or CR₂, where each R is independently H or alkyl (1-6C);

X is O, S, SO or SO₂; and

L is a flexible linker,

5 then Ar² is not a substituted or unsubstituted 6-membered aromatic ring;
if Ar¹ is

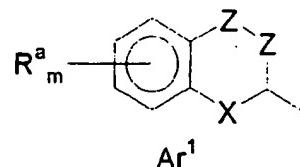


wherein R^a is a noninterfering substituent;

n is an integer of 0 and 5; and

10 L is a flexible linker which does not contain nitrogen or is a constrained linker,
then Ar² is not a substituted or unsubstituted phenyl or a substituted or
unsubstituted naphthyl.

4. The method of claim 2 with the further proviso that in the compound of
15 formula (1), if Ar¹ is



wherein R^a is a noninterfering substituent;

m is an integer of 0-4;

each dotted line represents an optional π-bond;

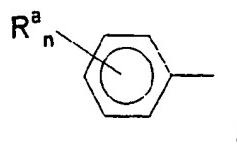
20 each Z is independently N, NR, O, S, CR or CR₂, where each R is
independently H or alkyl (1-6C);

X is O, S, SO or SO₂; and

L is a flexible linker,

then Ar² is not a substituted or unsubstituted 6-membered aromatic ring;

if Ar^1 is

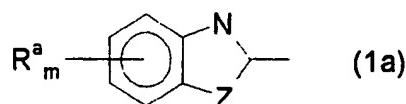


wherein R^a is a noninterfering substituent;

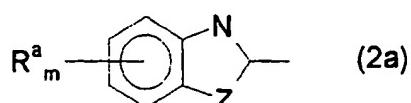
n is an integer of 0 and 5; and

5 L is a flexible linker which does not contain nitrogen or is a constrained linker,
then Ar^2 is not a substituted or unsubstituted phenyl or a substituted or
unsubstituted naphthyl.

5. The method of any of claims 1-4 wherein Ar^1 is



or



10

wherein each R^a is a noninterfering substituent;

m is an integer of 0-4;

the dotted line represents an optional π bond;

Z is O, S, NR or CR_2 in formula (1) or is CR in formula (2) where each R is

15 independently H or alkyl (1-6C); and

L is a flexible conjugating or nonconjugating linker or is a constrained linker.

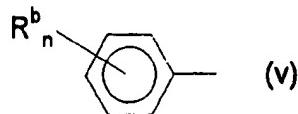
6. The method of claim 5 wherein L is a flexible conjugating or

nonconjugating linker.

20

7. The method of claim 6 wherein Z is NR.

8. The method of claim 7 wherein Ar² is a substituted or unsubstituted aromatic system containing a 5-membered heterocycle or is



wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
 5 L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or
 -CONR- where R is H or alkyl (1-6C); and/or
 the dotted line represents a π bond.

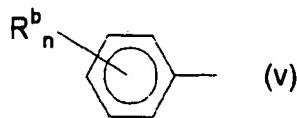
9. The method of claim 7 wherein each R^b is independently halo, OR, SR,
 10 NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an
 aromatic system.

10. The method of claim 7 wherein
 m is 0; and/or
 15 each R^b is independently OR, SR or halo;
 where n=2 and at least one R^b is OR or SR; and/or
 L is -NHCO- or -CR=CR-.

11. The method of claim 7 wherein said compound is 59-0100, 59-103,
 20 59-104, 59-105 or 59-106.

12. The method of claim 6 wherein Z is S.

13. The method of claim 12 wherein Ar² is a substituted or unsubstituted
 25 aromatic system containing a 6-membered heterocycle or is of the formula



wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
 L is $-N=N-$, $-N=CR-$, $-RC=CR-$, $-NRNR-$, $-CR_2NR-$, $-CR_2CR_2-$, $-NRCO-$ or
 $-CONR-$ where R is H or alkyl (1-6C); and/or

5 the dotted line represents a π bond.

14. The method of claim 13 wherein each R^b is independently halo, OR,
 SR , NR_2 , NO , NO_2 , OCF_3 or CF_3 wherein R is H or alkyl (1-6C) or R^b comprises an
aromatic system.

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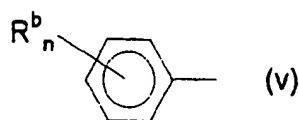
15. The method of claim 13 wherein
 m is 0; and/or
each R^b is independently OR, SR or halo;
where $n=2$ and at least one R^b is OR or SR; and/or
L is $-NHCO-$ or $-CR=CR-$.

16. The method of claim 12 wherein the compound is compound number
59-002, 59-0070, 59-0072, 59-0099, the benzothiazole counterpart of 59-0104,
59-0102, 59-0144, 59-0147, 59-0149, 59-0186, 59-0187, 59-0192, 59-0193, 59-0195,
20 59-0197, 59-0202, 59-0204, 59-0205, 59-0206, 59-0207, 59-0208, and 59-0210.

17. The method of claim 16 wherein the compound is the benzothiazole
counterpart of 59-0104, or is compound number 59-0147, 59-0205 or 59-0210.

25 18. The method of claim 6 wherein Z is CR or CR_2 .

19. The method of claim 18 wherein Ar^2 is



wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or

L is $-N=N-$, $-N=CR-$, $-RC=CR-$, $-NRNR-$, $-CR_2NR-$, $-CR_2CR_2-$, $-NRCO-$ or

$-CONR-$ where R is H or alkyl (1-6C); and/or

5 the dotted line represents a π bond.

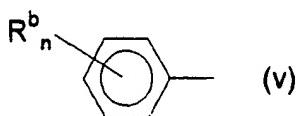
20. The method of claim 19 wherein each R^b is independently halo, OR,

SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

10

21. The method of claim 6 wherein Z is O.

22. The method of claim 21 wherein Ar² is of the formula



15 wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
 L is $-N=N-$, $-N=CR-$, $-RC=CR-$, $-NRNR-$, $-CR_2NR-$, $-CR_2CR_2-$, $-NRCO-$ or

$-CONR-$ where R is H or alkyl (1-6C); and/or

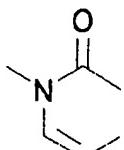
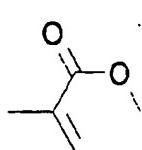
the dotted line represents a π bond.

20 23. The method of claim 19 wherein each R^b is independently halo, OR,
SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

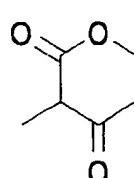
24. The method of claim 21 wherein the compound of formula (1) is
25 compound number 896-5005.

25. The method of claim 5 wherein L is a constrained linker.

26. The method of claim 25 wherein Z is S or NR; and/or
5 wherein L is selected from the group consisting of

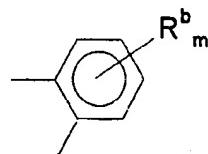


and



, and/or

wherein Ar² is



wherein R^b is a noninterfering substituent and m is 0-4.

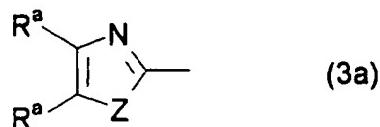
10

27. The method of claim 25 wherein each R^b is independently halo, OR,
SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or comprises an
aromatic system.

15

28. The method of claim 25 wherein the compound of formula (1) is
59-0124.

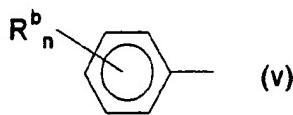
29. The method of any of claims 1-4 wherein Ar¹ is of the formula



20

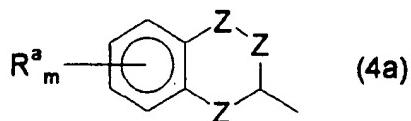
wherein each R^a is independently a noninterfering substituent or is H; and
Z is NR, S or O, wherein R is alkyl (1-6C) or H.

30. The method of claim 29 wherein Z is S; and/or
wherein Ar² is



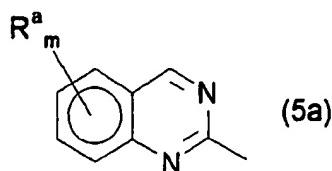
5 wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
L is -N=N-, -N=CR-, -RC=CR-, -NRNR-, -CR₂NR-, -CR₂CR₂-, -NRCO- or
-CONR- where R is H or alkyl (1-6C); and/or
the dotted line represents a π bond; and/or
each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein
10 R is H or alkyl (1-6C) or comprises an aromatic system.

31. The method of any of claims 1-4 wherein Ar¹ is

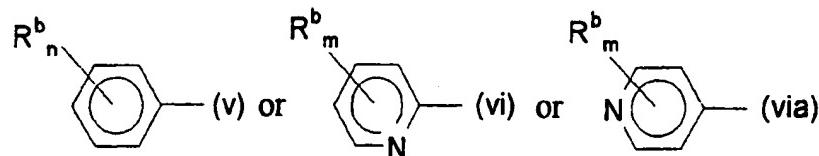


15 wherein R^a is a noninterfering substituent;
m is an integer of 0-4;
each dotted line represents an optional π-bond;
each Z is independently N, NR, CR or CR₂, where each R is independently H
or alkyl (1-6C) with the proviso that at least one Z is N or NR.

20 32. The method of claim 31 wherein Ar¹ is



33. The method of claim 31 wherein Ar₂ is



wherein each R^b is independently a noninterfering substituent, and n is 0-5 and m is 0-4; and/or

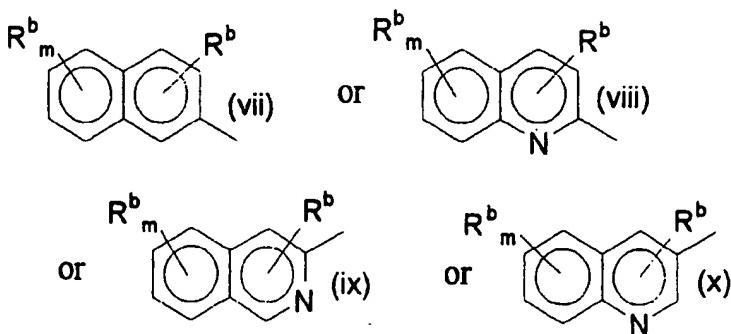
5 L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NRCR₂CR₂-,
 -NRCR₂CO-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or
 -NRCOCR₂NR-.

10 34. The method of claim 33 wherein each R^b is independently halo, OR,
 SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an
 aromatic system.

15 35. The method of claim 32 wherein
 each R^b is NR₂ or OR and m and n are 0, 1 or 2; and/or
 L is -CR=CR-, -N=N- or -NRCO-.

20 36. The method of claim 35 wherein the compound of formula (1) is
 59-0030, 59-0078, 59-0091, 59-0093, 59-0150, 50-0197, 59-0198, 59-0199 or
 59-0480.

37. The method of claim 31 wherein Ar₂ is substituted or unsubstituted
 quinolyl or naphthyl of the formula

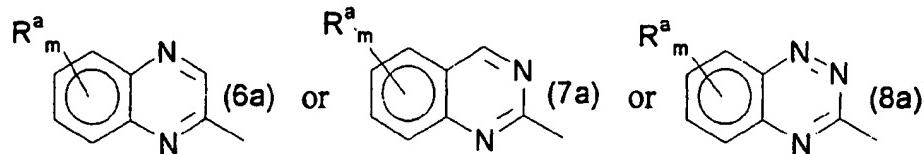


wherein each R^b is a noninterfering substituent and m is 0-4.

38. The method of claim 37 wherein L is -N=N-, -RC=CR-, -RC=N-,
 5 -NRCO-, -NRCR₂-, -NR₂CR₂-, -NR₂CO-, -NRNR-, -CR₂CR₂-,
 -NR₂CR₂CR₂NR-, -NR₂CR=CRNR- or -NR₂COCR₂NR-; and/or
 wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃
 wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and m is 0, 1 or 2.

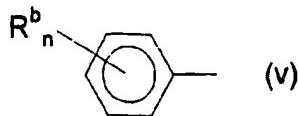
- 10 39. The method of claim 38 wherein the compound of formula (1) is
59-0089, 59-0090, 59-0092 or 59-0094.

40. The method of claim 31 wherein Ar¹ is



- 15 wherein each R^a is a noninterfering substituent and m is 0-4.

41. The method of claim 40 wherein L is -N=N-, -RC=CR-, -RC=N-,
-NRCO-, -NRCR₂-, -NR₂CR₂-, -NR₂CO-, -NRNR-, -CR₂CR₂-,
-NR₂CR₂NR-, -NR₂CR=CRNR- or -NRCO₂CR₂NR-; and/or
20 Ar² is



wherein R^b is a noninterfering substituent and n is an integer of 0-5; and/or
wherein each R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃ or CF₃
wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system.

5

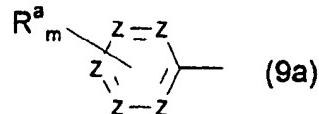
42. The method of claim 41 wherein the compound of formula (1) is
59-203, 59-285 or 59-286.

10

43. The method of claim 31 wherein L is a constrained linker.

10

44. The method of any of claims 1-4 wherein Ar¹ is



wherein each R^a is independently a noninterfering substituent;
 m is an integer of 0-4;

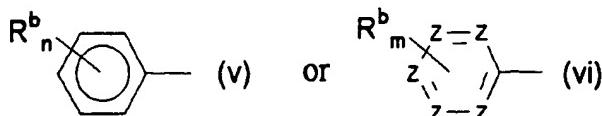
each Z is independently N or CR, where R is H or alkyl (1-6C), with the
proviso that at least one Z must be N and at least one Z must be CR.

15

45. The method of claim 44 wherein L is a flexible conjugating or
nonconjugating linker; and/or

20

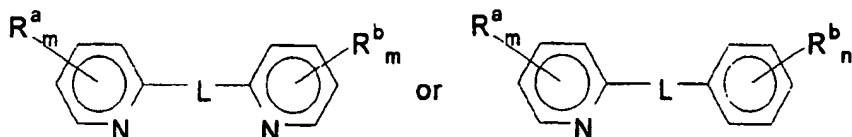
wherein Ar² is



wherein each R^b is independently a noninterfering substituent, and

in (vi) each Z is independently N or CR, where R is H or alkyl (1-6C), with the proviso that at least one Z must be a N and at least one Z must be CR.

46. The method of claim 45 wherein the compound of formula (1) is of the
5 formula

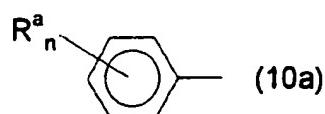


47. The method of claim 46 wherein L is -N=N-, -RC=CR-, -RC=N-,
-NRCO-, -NRCR₂-, -NRCR₂CR₂-, -NRCR₂CO-, -NRNR-, -CR₂CR₂-,
10 -NRCR₂CR₂NR-, -NRCR=CRNR- or -NRCOOCR₂NR-, and/or
wherein each R^a and R^b is independently halo, OR, SR, NR₂, NO, NO₂, OCF₃
or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an aromatic system and each m
and n is independently 0, 1 or 2.

- 15 48. The method of claim 47 wherein L is -NHCR₂CR₂NH-, m is 1 and R^a is
CF₃ para to L.

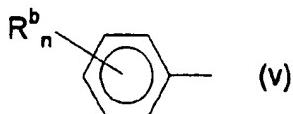
49. The method of claim 48 wherein the compound of formula (1) is
59-0145, 59-0450, 59-0459 or 59-0483.

- 20 50. The method of any of claims 1-4 wherein Ar¹ is



- wherein each R^a is a noninterfering substituent; and
n is an integer of 0 and 5, and
25 wherein L is a flexible linker that contains at least one nitrogen; and/or

wherein Ar² is of the formula



- and L is -N=N-, -RC=CR-, -RC=N-, -NRCO-, -NRCR₂-, -NR₂CR₂-,
 -NRCR₂CO-, -NRNRCR₂CR₂-, -NRNRCR=CR-, -NRNRCOCR₂-,
 5 -NRNRCOCR=CR-, -NRNRCSCR₂-, -NRNRCSCR=CR-, -NRNRCNR-,
 -NRNRCNSR-, -NRNR-, -CR₂CR₂-, -NRCR₂CR₂NR-, -NRCR=CRNR- or
 -NRCOCR₂NR-.

51. The method of claim 50 wherein each R^b is independently halo, OR,
 10 SR, NR₂, NO, NO₂, OCF₃ or CF₃ wherein R is H or alkyl (1-6C) or R^b comprises an
 aromatic system.

52. The method of claim 50 wherein L is -CR=CRCONRNR-,
 -CR=CRCNSNRNR-, -CR₂CONRNR-, -CR₂CSNMRNR-, -NRNRCNR- or
 15 -NRNRCNSR- and/or
 R^b is -NR₂ and n=1 wherein R^b is in the para position.

53. The method of claim 50 wherein R^a is -COOR and m is 1.
 20 54. The method of claim 52 wherein the compound of formula (1) is
 59-0045, 59-0095, 59-0096, 59-0097 or 59-0098.

55. A pharmaceutical composition for use in a method to treat a condition
 in a vertebrate animal characterized by a deficiency in, or need for, bone growth
 25 replacement and/or an undesirable level of bone resorption which composition contains
 a pharmaceutically acceptable excipient and an effective amount of a compound of the
 formula set forth in any preceding claim.

56. A compound for use in preparing a composition for use in the treatment
of a condition in a vertebrate animal characterized by a deficiency in, or need for, bone
growth replacement and/or an undesirable level of bone resorption which method
comprises administering said composition to a vertebrate subject, said compound set
5 forth in any preceding claim.

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Ar^1 - linker - Ar^2 1.5 - 15 Å		(I)
Ar^1	Ar^2	
contains 5-membered heterocycle	substituted or unsubstituted benzene	II-A
contains 5-membered heterocycle	substituted or unsubstituted naphthalene	II-B
contains 5-membered heterocycle	contains 6-membered heterocycle	II-C
contains 5-membered heterocycle	contains 5-membered heterocycle	II-D
contains 6-membered heterocycle	substituted or unsubstituted benzene	II-E
contains 6-membered heterocycle	substituted or unsubstituted naphthalene	II-F
contains 6-membered heterocycle	contains 6-membered heterocycle	II-G
substituted or unsubstituted naphthalene	substituted or unsubstituted benzene	II-H
substituted or unsubstituted naphthalene	substituted or unsubstituted naphthalene	II-I
substituted or unsubstituted benzene	substituted or unsubstituted benzene	II-J

Figure 1

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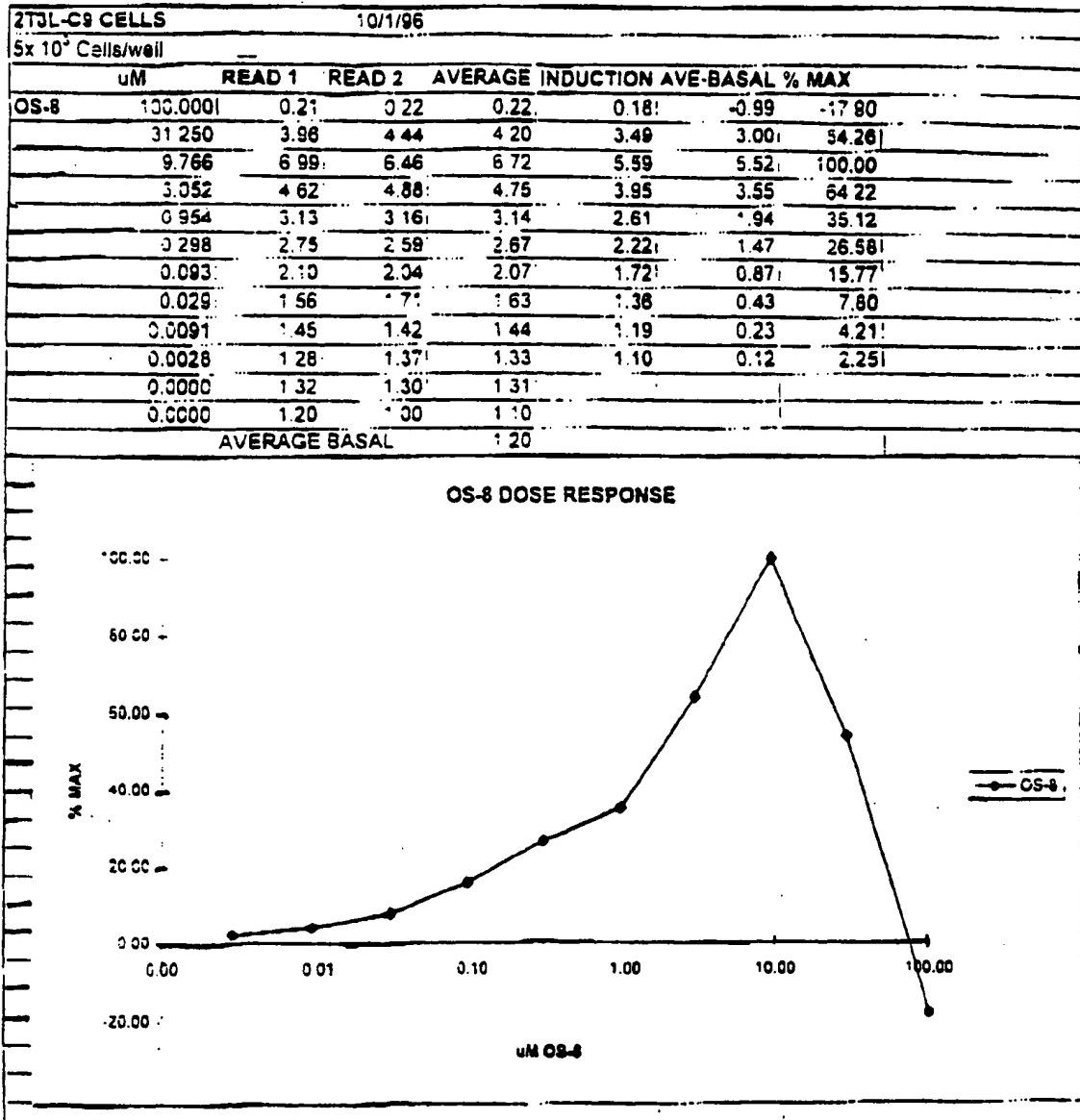


Figure 2

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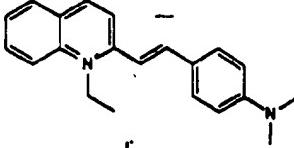
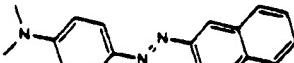
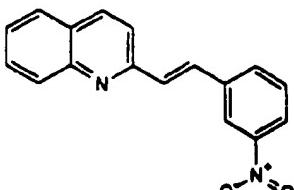
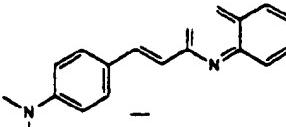
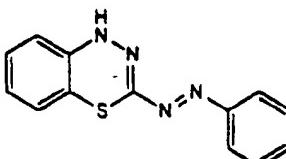
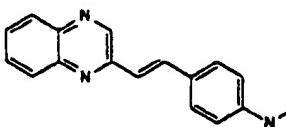
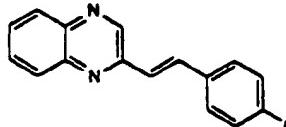
NNC#	MOL.WEIGHT	Concentration	% Response
			
50-0194	430.33		
50-0194	100.00 μM	-19.190	
	31.25 μM	32.450	
	9.77 μM	-14.240	
	3.05 μM	-11.330	
	953.67 nM	-12.780	
	298.02 nM	-13.450	
	93.13 nM	-12.280	
	29.10 nM	-9.440	
	9.09 nM	-6.480	
	2.84 nM	-8.130	
	888.18 pM	-3.320	
			
50-0195	275.36		
50-0195	100.00 μM	-4.630	
	31.25 μM	16.790	
	9.77 μM	62.830	
	3.05 μM	102.720	
	953.67 nM	60.660	
	298.02 nM	32.450	
	93.13 nM	19.340	
	29.10 nM	17.220	
	9.09 nM	5.640	
	2.84 nM	4.640	
	888.18 pM	5.640	
			
50-0196	276.30		
50-0196	100.00 μM	-16.210	
	31.25 μM	-8.560	
	9.77 μM	11.620	
	3.05 μM	27.780	
	953.67 nM	16.390	
	298.02 nM	6.230	
	93.13 nM	12.420	
	29.10 nM	12.830	
	9.09 nM	6.590	
	2.84 nM	7.970	
	888.18 pM	5.060	

Figure 3

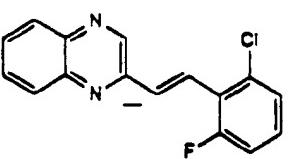
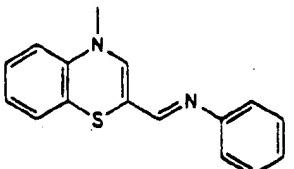
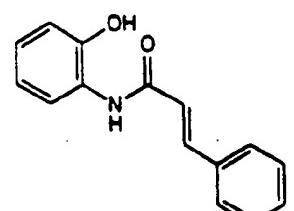
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59-0197	274.37			
59-0197		100.00 μM	-18.250	
		31.25 μM	-14.880	
		9.77 μM	4.040	
		3.05 μM	93.780	
		953.67 nM	205.530	
		298.02 nM	242.820	
		93.13 nM	195.880	
		29.10 nM	115.320	
		9.09 nM	65.630	
		2.84 nM	54.380	
		888.18 pM	33.180	
				
59-0008	254.32			
				
59-0019	59-0019			
59-0019		100.00 μM	-22.240	
		31.25 μM	-22.670	
		9.77 μM	-17.470	
		3.05 μM	74.480	
		953.67 nM	198.080	
		298.02 nM	258.340	
		93.13 nM	225.350	
		29.10 nM	75.220	
		9.09 nM	24.030	
		2.84 nM	34.480	
		888.18 pM	-3.740	
				
59-0020	286.73			
59-0020		100.00 μM	-18.510	
		31.25 μM	-18.040	
		9.77 μM	-0.270	
		3.05 μM	89.490	
		953.67 nM	153.320	
		298.02 nM	110.240	
		93.13 nM	60.030	

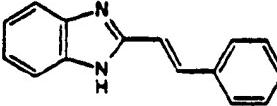
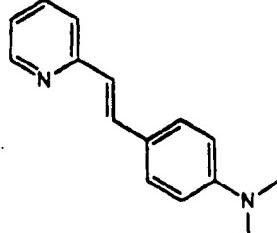
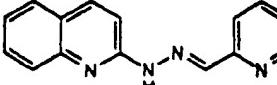
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	29.10 nM	37.870
	9.09 nM	24.820
	2.84 nM	20.500
	688.18 pM	13.310

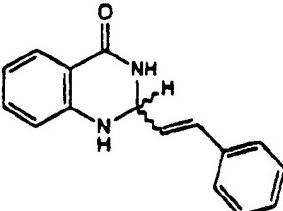
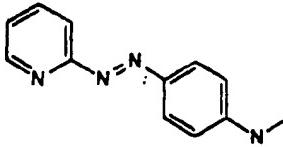
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59-0021	284.72			
59-0021	100.00 μM	-16.310		
	31.25 μM	-12.850		
	9.77 μM	84.130		
	3.05 μM	89.940		
	953.67 nM	65.750		
	298.02 nM	33.940		
	93.13 nM	22.560		
	29.10 nM	25.020		
	9.09 nM	13.910		
	2.84 nM	33.270		
	888.18 pM	15.500		
				
59-0022	268.37			
59-0022	100.00 μM	7.250		
	31.25 μM	-2.070		
	9.77 μM	-0.270		
	3.05 μM	4.390		
	953.67 nM	3.060		
	298.02 nM	-1.800		
	93.13 nM	-0.200		
	29.10 nM	-3.270		
	9.09 nM	1.130		
	2.84 nM	2.560		
	888.18 pM	2.460		
				
59-0023	239.28			
59-0023	100.00 μM	-12.720		
	31.25 μM	33.140		
	9.77 μM	58.500		
	3.05 μM	29.550		
	953.67 nM	25.360		
	298.02 nM	15.700		
	93.13 nM	7.380		
	29.10 nM	-9.710		
	9.09 nM	1.000		
	2.84 nM	4.520		
	888.18 pM	-0.010		

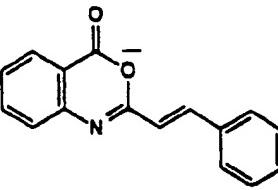
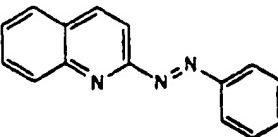
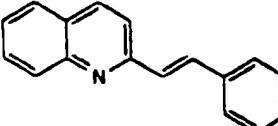
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59-0024	220.28				
					
59-0025	224.31				
59-0025		100.00 μM	-25.590		
		31.25 μM	14.150		
		9.77 μM	50.890		
		3.05 μM	57.880		
		953.67 nM	38.900		
		298.02 nM	28.530		
		93.13 nM	19.680		
		29.10 nM	17.490		
		9.09 nM	-0.600		
		2.84 nM	-4.190		
		888.18 pM	4.870		
					
59-0026	248.29				
59-0026		100.00 μM	-29.830		
		31.25 μM	-9.440		
		9.77 μM	-10.470		
		3.05 μM	48.220		
		953.67 nM	107.760		
		298.02 nM	86.720		
		93.13 nM	36.850		
		29.10 nM	26.720		
		9.09 nM	8.520		
		2.84 nM	-1.240		
		888.18 pM	4.020		

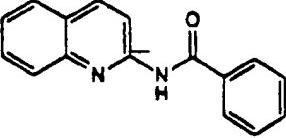
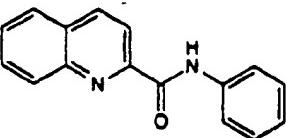
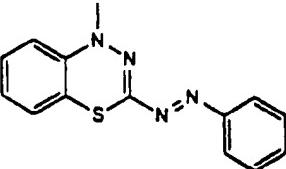
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59-0027	250.30					
59-0027		100.00 μM	89.810			
		31.25 μM	54.670			
		9.77 μM	44.940			
		3.05 μM	23.780			
		953.67 nM	8.380			
		298.02 nM	6.330			
		93.13 nM	7.360			
		29.10 nM	3.380			
		9.09 nM	-1.620			
		2.84 nM	-3.670			
		888.18 pM	-0.720			
						
59-0028	226.28					
59-0028		100.00 μM	-26.750			
		31.25 μM	-16.740			
		9.77 μM	29.550			
		3.05 μM	100.580			
		953.67 nM	54.940			
		298.02 nM	31.340			
		93.13 nM	7.500			
		29.10 nM	7.500			
		9.09 nM	7.880			
		2.84 nM	3.140			
		888.18 pM	4.670			

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59-0029	249.27			
59-0029		100.00 μM	-15.160	
		31.25 μM	41.940	
		9.77 μM	36.630	
		3.05 μM	7.120	
		953.67 nM	21.880	
		298.02 nM	15.540	
		93.13 nM	1.810	
		29.10 nM	1.370	
		9.09 nM	12.140	
		2.84 nM	-4.230	
		888.18 pM	9.040	
				
59-0030A	233.28			
59-0030 A		100.00 μM	-27.970	
		31.25 μM	-22.830	
		9.77 μM	-5.420	
		3.05 μM	57.280	
		953.67 nM	72.620	
		298.02 nM	53.000	
		93.13 nM	29.990	
		29.10 nM	14.630	
		9.09 nM	3.870	
		2.84 nM	6.970	
		888.18 pM	1.810	
				
59-0031	231.30			
59-0031		100.00 μM	-25.790	
		31.25 μM	-17.810	
		9.77 μM	20.840	
		3.05 μM	87.380	
		953.67 nM	49.320	
		298.02 nM	43.110	
		93.13 nM	29.830	
		29.10 nM	1.810	
		9.09 nM	1.220	
		2.84 nM	-0.550	
		888.18 pM	4.160	

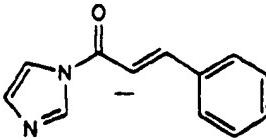
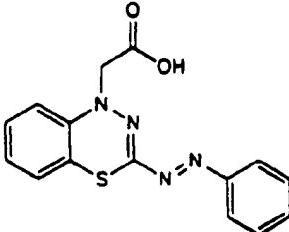
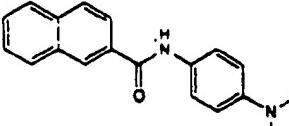
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59-0032	248.29				
59-0032		100.00 μM	-7.780		
		31.25 μM	40.750		
		9.77 μM	42.820		
		3.05 μM	25.700		
		953.67 nM	31.170		
		298.02 nM	34.410		
		93.13 nM	3.570		
		29.10 nM	4.320		
		9.09 nM	-10.000		
		2.84 nM	5.650		
		888.18 pM	11.990		
					
59-0033	248.29				
59-0033		100.00 μM	-28.180		
		31.25 μM	-11.590		
		9.77 μM	55.300		
		3.05 μM	49.710		
		953.67 nM	47.410		
		298.02 nM	0.250		
		93.13 nM	7.980		
		29.10 nM	-8.940		
		9.09 nM	-7.630		
		2.84 nM	-0.400		
		888.18 pM	-5.980		
					
59-0034	268.34				
59-0034		100.00 μM	-28.51		
		31.25 μM	24		
		9.77 μM	73.58		
		3.05 μM	37.91		
		953.67 nM	20.09		
		298.02 nM	16.87		
		93.13 nM	15.23		
		29.10 nM	28.83		
		9.09 nM	9.08		
		2.84 nM	-23.02		
		888.18 pM	-0.32		

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<chem>CN(c1ccc(C(=O)Nc2cc3ccccc3n2)cc1)C</chem>				
59-0035	291.36			
59-0035	100.00 μM	-14.92		
	31.25 μM	29.17		
	9.77 μM	15.87		
	3.05 μM	18.81		
	953.67 nM	3.88		
	298.02 nM	6.15		
	93.13 nM	3.22		
	29.10 nM	-10.03		
	9.09 nM	15.58		
	2.84 nM	-3.58		
	888.18 pM	-7.13		
<chem>CNCC(=O)c1cc2ccccc2n1</chem>				
59-0036	262.31			
59-0036	100.00 μM	-0.88		
	31.25 μM	-3.25		
	9.77 μM	-4.54		
	3.05 μM	-1.95		
	953.67 nM	0.32		
	298.02 nM	-6.48		
	93.13 nM	-17.19		
	29.10 nM	-0.68		
	9.09 nM	-5.52		
	2.84 nM	-9.41		
	888.18 pM	-16.53		
<chem>CN1C(=O)C(O)=C2=C1Cc3ccccc3N=C2C(=O)Nc4ccccc4</chem>				
59-0037	308.00			
59-0037	100.00 μM	-10.69		
	31.25 μM	-11.89		
	9.77 μM	-10.03		
	3.05 μM	-19.11		
	953.67 nM	-9.41		
	298.02 nM	2.27		
	93.13 nM	-2.91		
	29.10 nM	-10.69		
	9.09 nM	2.59		
	2.84 nM	-0.66		
	888.18 pM	-2.59		

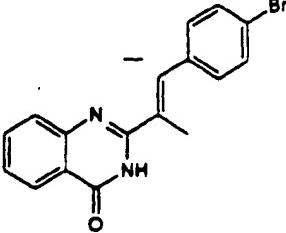
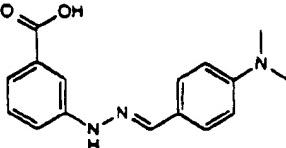
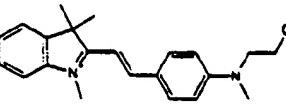
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59-0038	291.36			
59-0038	100.00 μM	-23.430		
	31.25 μM	-8.380		
	9.77 μM	-0.100		
	3.05 μM	-2.880		
	953.67 nM	-2.240		
	298.02 nM	3.900		
	93.13 nM	6.350		
	29.10 nM	1.150		
	9.09 nM	6.980		
	2.84 nM	-4.390		
	888.18 pM	-0.380		
				
59-0039	312.35			
59-0039	100.00 μM	14.170		
	31.25 μM	7.620		
	9.77 μM	1.940		
	3.05 μM	-3.140		
	953.67 nM	-7.770		
	298.02 nM	-5.980		
	93.13 nM	-8.620		
	29.10 nM	-2.390		
	9.09 nM	-16.580		
	2.84 nM	-4.480		
	888.18 pM	-0.450		
				
59-0040	290.37			
59-0040	100.00 μM	-20.400		
	31.25 μM	-17.310		
	9.77 μM	-0.110		
	3.05 μM	32.180		
	953.67 nM	36.180		
	298.02 nM	17.440		
	93.13 nM	2.040		
	29.10 nM	10.350		
	9.09 nM	-4.070		
	2.84 nM	6.980		
	888.18 pM	13.440		

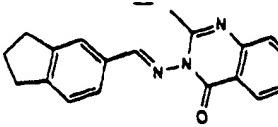
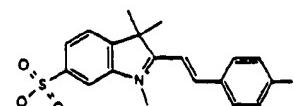
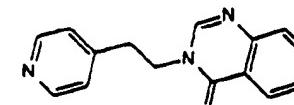
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<chem>CN(CCC)CCCCNc1nc(Cl)c2ccccc2n1=CC=C(c3ccccc3Br)C=C3</chem>				
59-0041	501.90			
59-0041	100.00 μM	-18.37		
	31.25 μM	-17.33		
	9.77 μM	-5.11		
	3.05 μM	3.31		
	953.67 nM	-0.77		
	298.02 nM	-1.56		
	93.13 nM	3.55		
	29.10 nM	-11.24		
	9.09 nM	0.25		
	2.84 nM	-0.27		
	888.18 pM	2.02		
<chem>O=C1NC(=O)c2ccccc2N1Cc3ccccc3</chem>				
59-0042	281.36			
59-0042	100.00 μM	163.51		
	31.25 μM	-7.67		
	9.77 μM	9.41		
	3.05 μM	0.75		
	953.67 nM	6.11		
	298.02 nM	3.82		
	93.13 nM	2.54		
	29.10 nM	4.07		
	9.09 nM	-9.73		
	2.84 nM	-0.02		
	888.18 pM	18.37		
<chem>CCN1C=CC=C1C(=O)N2C(=O)N(c3ccccc3)C(=N)N2c4ccccc4</chem>				
59-0043	280.29			
59-0043	100.00 μM	20.66		
	31.25 μM	7.4		
	9.77 μM	-1.29		
	3.05 μM	-2.31		
	953.67 nM	1.54		
	298.02 nM	-0.79		
	93.13 nM	1.52		
	29.10 nM	2.79		
	9.09 nM	-0.27		
	2.84 nM	8.92		
	888.18 pM	-4.34		

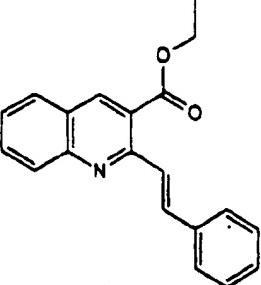
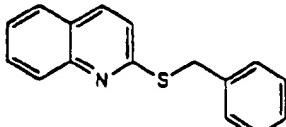
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59-0044	341.21			
59-0044	100.00 μM	7.38		
	31.25 μM	11.72		
	9.77 μM	12.49		
	3.05 μM	-0.52		
	953.67 nM	0.5		
	298.02 nM	6.11		
	93.13 nM	-1.54		
	29.10 nM	19.14		
	9.09 nM	7.13		
	2.84 nM	-2.06		
	888.18 pM	5.84		
				
59-0045	283.33			
59-0045	100.00 μM	52.37	64.480	
	31.25 μM	148.43	192.960	
	9.77 μM	204.47	422.540	
	3.05 μM	280.31	437.020	
	953.67 nM	254.62	410.890	
	298.02 nM	218.21	266.090	
	93.13 nM	196.98	183.730	
	29.10 nM	96.06	80.440	
	9.09 nM	67.35	55.530	
	2.84 nM	52.99	44.160	
				
59-0046	389.37			
59-0046	100.00 μM	79.33		
	31.25 μM	2.24		
	9.77 μM	-1.67		
	3.05 μM	-6.18		
	953.67 nM	0.001		
	298.02 nM	-3.63		
	93.13 nM	-0.84		
	29.10 nM	-8.42		
	9.09 nM	-3.92		
	2.84 nM	0.3		
	888.18 pM	5.61		

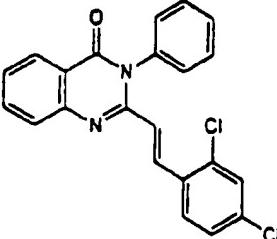
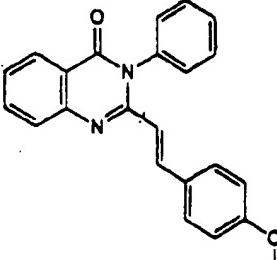
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59-0047	303.37			
59-0047		100.00 μM	-6.73	
		31.25 μM	10.38	
		9.77 μM	-6.18	
		3.05 μM	-1.39	
		953.67 nM	-10.11	
		298.02 nM	-4.49	
		93.13 nM	-7.28	
		29.10 nM	-12.34	
		9.09 nM	-3.08	
		2.84 nM	-2.26	
		888.18 pM	-5.34	
				
59-0048	384.50			
59-0048		100.00 μM	-6.73	
		31.25 μM	0.27	
		9.77 μM	-5.61	
		3.05 μM	-2.26	
		953.67 nM	-12.89	
		298.02 nM	-1.69	
		93.13 nM	-4.77	
		29.10 nM	-8.14	
		9.09 nM	-3.92	
		2.84 nM	-11.21	
		888.18 pM	-4.77	
				
59-0049	251.29			
59-0049		100.00 μM	4.49	
		31.25 μM	0	
		9.77 μM	-4.77	
		3.05 μM	1.96	
		953.67 nM	8.69	
		298.02 nM	-5.04	
		93.13 nM	-2.24	
		29.10 nM	1.69	
		9.09 nM	-4.49	
		2.84 nM	2.24	
		888.18 pM	-0.31	

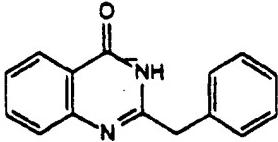
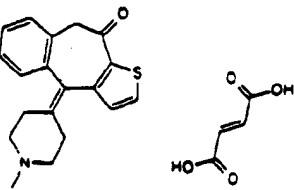
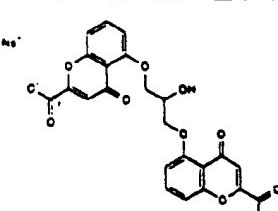
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	59-0050	303.36				
59-0050		100.00 μM	45.79			
		31.25 μM	10.02			
		9.77 μM	11.29			
		3.05 μM	-4.68			
		953.67 nM	-6.92			
		298.02 nM	-5.65			
		93.13 nM	1.69			
		29.10 nM	-7.57			
		9.09 nM	-12.05			
		2.84 nM	-13.63			
		888.18 pM	5.2			
	59-0051	251.35				
59-0051		100.00 μM	32.38			
		31.25 μM	-18.42			
		9.77 μM	-0.59			
		3.05 μM	-13.94			
		953.67 nM	-12.02			
		298.02 nM	-14.59			
		93.13 nM	-7.55			
		29.10 nM	-11.4			
		9.09 nM	-14.91			
		2.84 nM	-10.74			
		888.18 pM	-20.03			

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59-0052	393.28			
59-0052	100.00 μM	-21.62		
	31.25 μM	-13.32		
	9.77 μM	-21.31		
	3.05 μM	-11.08		
	953.67 nM	-20.66		
	298.02 nM	-17.14		
	93.13 nM	-16.49		
	29.10 nM	-11.4		
	9.09 nM	-10.74		
	2.84 nM	-11.08		
	888.18 pM	-14.59		
				
59-0053	354.41			
59-0053	100.00 μM	-17.14		
	31.25 μM	-21.31		
	9.77 μM	-9.47		
	3.05 μM	-11.08		
	953.67 nM	-0.83		
	298.02 nM	-11.41		
	93.13 nM	-9.47		
	29.10 nM	-19.72		
	9.09 nM	-18.45		
	2.84 nM	-10.09		
	888.18 pM	-2.76		

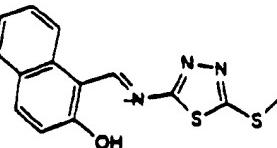
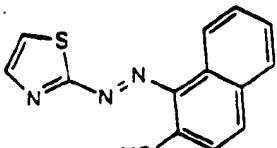
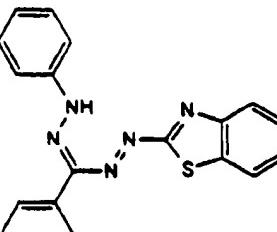
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59-0054	236.28			
59-0054	100.00 μM	-20.04		
	31.25 μM	-6.95		
	9.77 μM	8.31		
	3.05 μM	-3.37		
	953.67 nM	-2.41		
	298.02 nM	-0.99		
	93.13 nM	-0.99		
	29.10 nM	-1.94		
	9.09 nM	5.92		
	2.84 nM	-2.17		
	888.18 pM	-9.31		
				
59-0055	425.51			
59-0055	100.00 μM	-13.76		
	31.25 μM	-9.51		
	9.77 μM	-2.02		
	3.05 μM	3.24		
	953.67 nM	-6.27		
	298.02 nM	-4.05		
	93.13 nM	-1.62		
	29.10 nM	-7.49		
	9.09 nM	-7.09		
	2.84 nM	-3.04		
				
59-0056	512.34			
59-0056	100.00 μM	-1.42		
	31.25 μM	-4.87		
	9.77 μM	0.18		
	3.05 μM	3.64		
	953.67 nM	-6.07		
	298.02 nM	-7.29		
	93.13 nM	0.001		
	29.10 nM	-4.25		
	9.09 nM	-1.02		
	2.84 nM	-3.85		

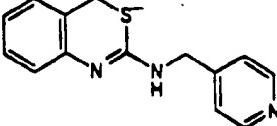
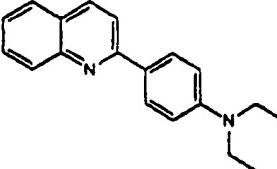
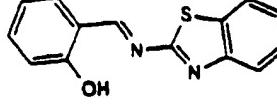
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<chem>CN1C=NC2=C1SC3=C(C=C2)Nc4ccccc4S3</chem>				
59-0057				
59-0057	100.00 μ M	-24.150		
	31.25 μ M	-24.300		
	9.77 μ M	-5.880		
	3.05 μ M	-11.500		
	953.67 nM	-13.000		
	298.02 nM	-6.280		
	93.13 nM	-12.550		
	29.10 nM	-6.870		
	9.09 nM	-8.520		
	2.84 nM	-16.290		
<chem>COc1cc2c(cc1S(=O)(=O)N=C(c3ccccc3)c4ccccc4)nc2</chem>				
59-0058				
59-0058	100.00 μ M	4.170		
	31.25 μ M	7.620		
	9.77 μ M	-1.790		
	3.05 μ M	-7.320		
	953.67 nM	-1.940		
	298.02 nM	-6.870		
	93.13 nM	-1.490		
	29.10 nM	-8.370		
	9.09 nM	-5.080		
	2.84 nM	-12.400		
<chem>CC1=CSC2=C1SC3=C(N=C4C=C(Cl)C=C4)C=C3</chem>				
59-0059				
59-0059	100.00 μ M	-18.770		
	31.25 μ M	-18.140		
	9.77 μ M	-3.090		
	3.05 μ M	0.150		
	953.67 nM	6.010		
	298.02 nM	-1.910		
	93.13 nM	-1.780		
	29.10 nM	-9.100		
	9.09 nM	-8.220		
	2.84 nM	-5.720		

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59-0060				
	100.00 μM	-4.250		
	31.25 μM	-14.520		
	9.77 μM	1.030		
	3.08 μM	-1.160		
	953.67 nM	-13.200		
	298.02 nM	-0.740		
	93.13 nM	-3.670		
	29.10 nM	-7.340		
	9.09 nM	-1.310		
	2.84 nM	0.290		
				
59-0061				
	100.00 μM	-17.890		
	31.25 μM	-18.770		
	9.77 μM	-17.170		
	3.08 μM	-14.080		
	953.67 nM	-17.020		
	298.02 nM	-7.190		
	93.13 nM	-1.910		
	29.10 nM	-0.440		
	9.09 nM	-6.010		
	2.84 nM	-4.560		
				
59-0062				
	100.00 μM	-13.940		
	31.25 μM	-12.910		
	9.77 μM	-4.580		
	3.08 μM	-4.540		
	953.67 nM	-6.900		
	298.02 nM	-4.100		
	93.13 nM	-1.620		
	29.10 nM	3.230		

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		9.09nM	8.070
		2.84nM	0.440.
			
59-0063			
59-0063		100.00 μM	-2.510
		31.25 μM	-6.130
		9.77 μM	-8.950
		3.05 μM	-8.020
		953.67 nM	-8.010
		298.02 nM	-2.520
		93.13 nM	-5.810
		29.10 nM	-3.450
		9.09 nM	-4.390
		2.84 nM	-6.280
			
59-0064			
59-0064		100.00 μM	-23.090
		31.25 μM	-21.040
		9.77 μM	78.400
		3.05 μM	155.220
		953.67 nM	113.120
		298.02 nM	30.640
		93.13 nM	15.240
		29.10 nM	22.150
		9.09 nM	-0.770
		2.84 nM	4.410
			
59-0065			
59-0065		100.00 μM	-2.030
		31.25 μM	-2.980
		9.77 μM	-15.240
		3.05 μM	-15.400
		953.67 nM	-15.240
		298.02 nM	-10.520
		93.13 nM	-13.830
		29.10 nM	-5.810
		9.09 nM	-3.620
		2.84 nM	-7.070

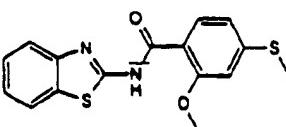
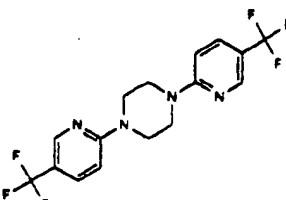
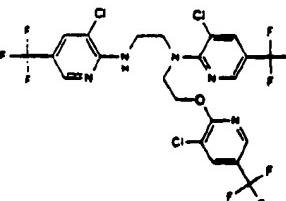
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<chem>CN(CCCc1ccccc1)c2ccccn2</chem>				
59-0066				
59-0066	100.00 μM	10.060		
	31.25 μM	2.680		
	9.77 μM	10.850		
	3.05 μM	14.610		
	953.67 nM	0.950		
	298.02 nM	3.780		
	93.13 nM	1.730		
	29.10 nM	-2.820		
	9.09 nM	-2.820		
	2.84 nM	-3.920		
<chem>CN(c1ccccc1)Cc2ncsc2</chem>				
59-0067				
59-0067	100.00 μM	-24.040		
	31.25 μM	-24.690		
	9.77 μM	-1.450		
	3.05 μM	60.900		
	953.67 nM	133.880		
	298.02 nM	75.330		
	93.13 nM	28.760		
	29.10 nM	20.070		
	9.09 nM	4.980		
	2.84 nM	4.440		
<chem>CN(c1ccccc1)Cc2ncsc2</chem>				
59-0068				
59-0068	100.00 μM	-22.130		
	31.25 μM	-7.880		
	9.77 μM	93.900		
	3.05 μM	81.080		
	953.67 nM	22.330		
	298.02 nM	17.300		
	93.13 nM	8.460		
	29.10 nM	-3.530		
	9.09 nM	-4.230		
	2.84 nM	-6.140		

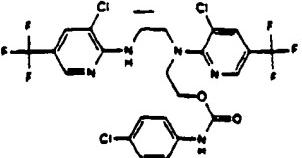
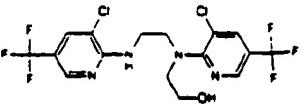
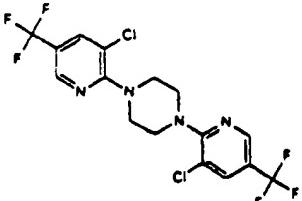
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<chem>O=C1OC(=O)c2cc(O)ccc2c1O</chem>				
59-0069				
59-0069	100.00 μ M	5.480		
	31.25 μ M	9.670		
	9.77 μ M	16.060		
	3.05 μ M	-7.180		
	953.67 nM	-2.840		
	298.02 nM	-3.710		
	93.13 nM	-11.180		
	29.10 nM	-5.790		
	9.09 nM	-7.180		
	2.84 nM	-4.750		
<chem>CN(C)c1ccc(C(=O)Nc2nc3ccccc3s2)cc1</chem>				
59-0070				
59-0070	100.00 μ M	-25.930		
	31.25 μ M	-23.000		
	9.77 μ M	36.060		
	3.05 μ M	214.280		
	953.67 nM	158.530		
	298.02 nM	72.890		
	93.13 nM	20.840		
	29.10 nM	7.760		
	9.09 nM	7.590		
	2.84 nM	-8.400		
<chem>CN(C)c1ccc(C(=O)Nc2cc3ccccc3n2)cc1</chem>				
59-0071				
59-0071	100.00 μ M	-18.650		
	31.25 μ M	-15.540		
	9.77 μ M	17.060		
	3.05 μ M	176.090		
	953.67 nM	76.070		
	298.02 nM	31.280		
	93.13 nM	16.410		
	29.10 nM	4.870		
	9.09 nM	-7.330		
	2.84 nM	-4.660		

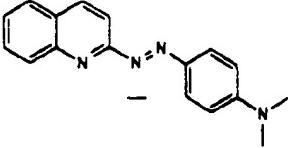
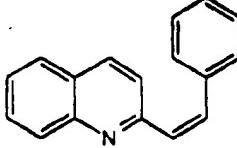
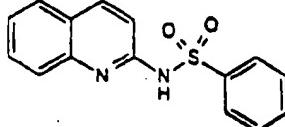
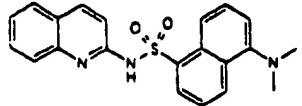
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59-0072				
59-0072	100.00 μM	-19.750		
	31.25 μM	-18.650		
	9.77 μM	-18.430		
	3.05 μM	-15.770		
	953.67 nM	9.970		
	298.02 nM	74.740		
	93.13 nM	178.430		
	29.10 nM	213.580		
	9.09 nM	164.320		
	2.84 nM	119.100		
	888.18 pM	60.770		
				
59-0073				
59-0073	100.00 μM	-3.010		
	31.25 μM	-4.830		
	9.77 μM	-9.660		
	3.05 μM	-4.680		
	953.67 nM	-6.500		
	298.02 nM	-2.510		
	93.13 nM	7.140		
	29.10 nM	0.97		
	9.09 nM	-5.5		
	2.84 nM	5.3		
				
59-0074				
59-0074	100.00 μM	-2.05		
	31.25 μM	2.14		
	9.77 μM	-4.85		
	3.05 μM	-3.5		
	953.67 nM	-4.85		
	298.02 nM	9.95		
	93.13 nM	4.47		
	29.10 nM	-6		
	9.09 nM	-4.17		
	2.84 nM	6.97		

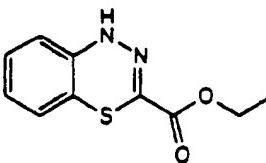
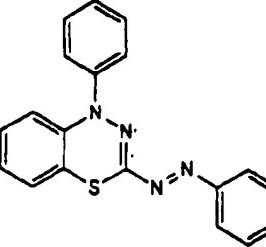
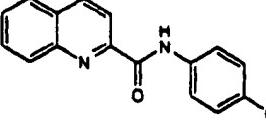
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59-0075				
59-0075	100.00 μM	-0.68		
	31.25 μM	-10.16		
	9.77 μM	-6.35		
	3.05 μM	-6.51		
	953.67 nM	-0.65		
	298.02 nM	5.97		
	93.13 nM	0.97		
	29.10 nM	-2.35		
	9.09 nM	0.32		
	2.84 nM	10.47		
				
59-0076				
59-0076	100.00 μM	-19.12		
	31.25 μM	9.29		
	9.77 μM	10.63		
	3.05 μM	22.43		
	953.67 nM	19.93		
	298.02 nM	3.47		
	93.13 nM	19.93		
	29.10 nM	10.63		
	9.09 nM	14.28		
	2.84 nM	11.3		
				
59-0077				
59-0077	100.00 μM	-20.96		
	31.25 μM	-16.23		
	9.77 μM	-10.58		
	3.05 μM	-11.96		
	953.67 nM	-19.44		
	298.02 nM	-17.3		
	93.13 nM	-13.79		
	29.10 nM	-19.82		
	9.09 nM	-14.09		
	2.84 nM	-14.4		

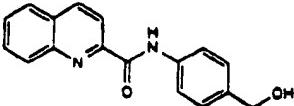
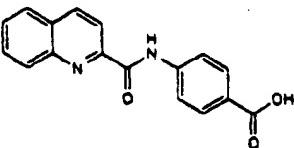
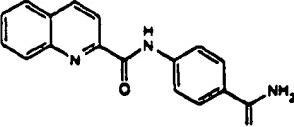
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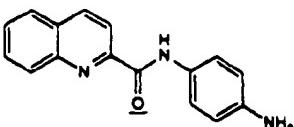
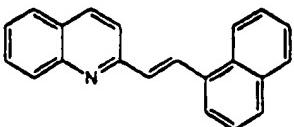
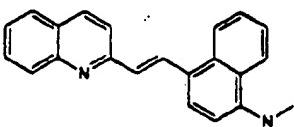
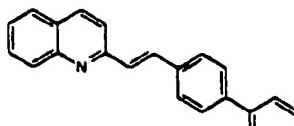
				
59-0078				
	100.00 μM	-26.940		
	31.25 μM	-22.560		
	9.77 μM	71.530		
	3.05 μM	207.980		
	953.67 nM	379.230		
	298.02 nM	241.460		
	93.13 nM	138.100		
	29.10 nM	84.020		
	9.09 nM	50.350		
	2.84 nM	56.600		
	0.80 nM	92.520		
				
59-0079				
59-0079	100.00 μM	-34.980		
	31.25 μM	-21.390		
	9.77 μM	37.200		
	3.05 μM	122.580		
	953.67 nM	69.010		
	298.02 nM	64.000		
	93.13 nM	48.490		
	29.10 nM	30.310		
	9.09 nM	33.490		
	2.84 nM	29.760		
				
59-0080				
59-0080	100.00 μM	5.380		
	31.25 μM	5.560		
	9.77 μM	6.440		
	3.05 μM	2.440		
	953.67 nM	-5.030		
	298.02 nM	7.680		
	93.13 nM	-3.630		
	29.10 nM	3.650		
	9.09 nM	1.050		
	2.84 nM	6.940		
				
59-0089				

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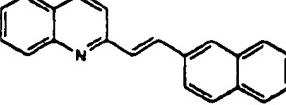
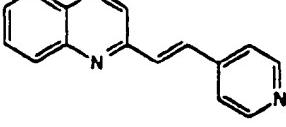
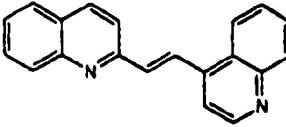
59-0081		100.00 μM	62.840
		31.25 μM	11.300
		9.77 μM	-8.670
		3.05 μM	2.440
		953.67 nM	-5.200
		298.02 nM	-2.080
		93.13 nM	1.220
		29.10 nM	-2.250
		9.09 nM	1.050
		2.84 nM	-3.300
			
59-0082		100.00 μM	111.79
		31.25 μM	62.68
		9.77 μM	32.38
		3.05 μM	9.11
		953.67 nM	-10.62
		298.02 nM	-1.66
		93.13 nM	-6.89
		29.10 nM	-3.91
		9.09 nM	2.22
		2.84 nM	16.36
			
59-0083		100.00 μM	48.93
		31.25 μM	40.91
		9.77 μM	25.85
		3.05 μM	17.85
		953.67 nM	8.55
		298.02 nM	3.9
		93.13 nM	2.05
		29.10 nM	7.99
		9.09 nM	-3.91
		2.84 nM	3.35
			
59-0084		100.00 μM	-37.670
		31.25 μM	26.050
		9.77 μM	9.210
		3.05 μM	10.070

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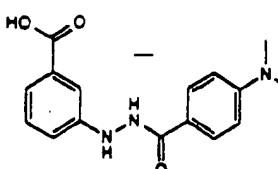
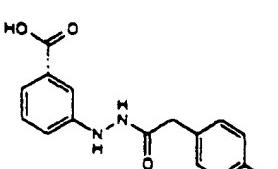
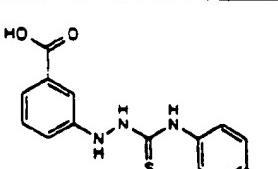
	953.67 nM	21.700
	298.02 nM	5.900
—	93.13 nM	4.870
	29.10 nM	-10.920
	9.09 nM	10.080
	2.84 nM	-2.080
		
59-0085		
	100.00 μM	17.070
	31.25 μM	41.690
	9.77 μM	18.500
	3.05 μM	20.340
	953.67 nM	22.490
	298.02 nM	8.090
	93.13 nM	11.790
	29.10 nM	1.240
	9.09 nM	-0.760
	2.84 nM	5.940
		
59-0086		
	100.00 μM	30.750
	31.25 μM	31.190
	9.77 μM	14.790
	3.05 μM	13.500
	953.67 nM	14.080
	298.02 nM	3.940
	93.13 nM	9.370
	29.10 nM	-2.610
	9.09 nM	-5.040
	2.84 nM	1.530
		
59-0087		
	100.00 μM	10.660
	31.25 μM	11.080
	9.77 μM	3.100
	3.05 μM	-1.320
	953.67 nM	17.070
	298.02 nM	7.950
	93.13 nM	-4.460
	29.10 nM	4.510
	9.09 nM	-0.470
	2.84 nM	9.660

				
59-0088				
59-0088	100.00 μ M			
	31.25 μ M			
	9.77 μ M			
	3.05 μ M			
	953.67 nM			
	298.02 nM			
	93.13 nM			
	29.10 nM			
	9.09 nM			
	2.84 nM			
				
59-0089				
59-0089	100.00 μ M	60.09		
	31.25 μ M	116.25		
	9.77 μ M	65.84		
	3.05 μ M	36.11		
	953.67 nM	37.96		
	298.02 nM	18.42		
	93.13 nM	6.33		
	29.10 nM	13.58		
	9.09 nM	0.75		
	2.84 nM	-5.77		
				
59-0090				
59-0090	100.00 μ M	32.77		
	31.25 μ M	24.63		
	9.77 μ M	18.51		
	3.05 μ M	41.31		
	953.67 nM	9.81		
	298.02 nM	-1.78		
	93.13 nM	3.53		
	29.10 nM	2.95		
	9.09 nM	2.95		
	2.84 nM	7.81		
				
59-0091				
59-0091	100.00 μ M	0.28		
	31.25 μ M	13.54		

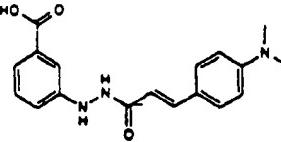
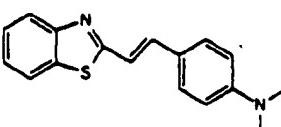
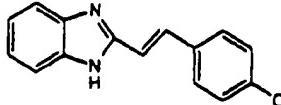
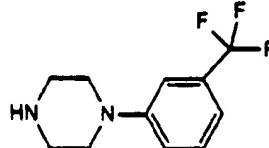
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		9.77 μ M	95.94
		3.05 μ M	87.71
		953.67 nM	44.17
		298.02 nM	38.26
		93.13 nM	23.87
		29.10 nM	21.65
		9.09 nM	10.95
		2.84 nM	20.92
			
59-0092			
59-0092		100.00 μ M	-11.56
		31.25 μ M	17.84
		9.77 μ M	50.19
		3.05 μ M	25.84
		953.67 nM	14.41
		298.02 nM	8.77
		93.13 nM	6.62
		29.10 nM	2.22
		9.09 nM	8.38
		2.84 nM	1
			
59-0093			
59-0093		100.00 μ M	-11.67
		31.25 μ M	15.02
		9.77 μ M	35.44
		3.05 μ M	29.69
		953.67 nM	22.88
		298.02 nM	19.56
		93.13 nM	5.18
		29.10 nM	7.39
		9.09 nM	4.56
		2.84 nM	5.9
			
59-0094			
59-0094		100.00 μ M	-17.69
		31.25 μ M	45.15
		9.77 μ M	24.97
		3.05 μ M	19.81
		953.67 nM	9.35
		298.02 nM	1.36
		93.13 nM	0.24
		29.10 nM	-0.48
		9.09 nM	6.16
		2.84 nM	1.61

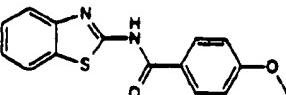
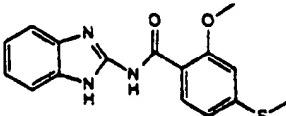
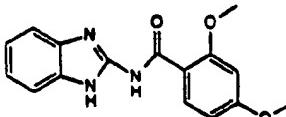
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59-0095				
59-0095	100.00 μM	44.7		
	31.25 μM	47.61		
	9.77 μM	12.78		
	3.05 μM	21.49		
	953.67 nM	15.01		
	298.02 nM	10.22		
	93.13 nM	13.98		
	29.10 nM	20.31		
	9.09 nM	10.9		
	2.84 nM	9.21		
				
59-0096				
59-0096	100.00 μM	413.05		
	31.25 μM	287.23		
	9.77 μM	137.38		
	3.05 μM	78.5		
	953.67 nM	49.13		
	298.02 nM	50.68		
	93.13 nM	47.95		
	29.10 nM	26.28		
	9.09 nM	18.75		
	2.84 nM	22.17		
				
59-0097				
59-0097	100.00 μM	77.47		
	31.25 μM	201.9		
	9.77 μM	160.93		
	3.05 μM	61.44		
	953.67 nM	47.78		
	298.02 nM	51.54		
	93.13 nM	34.64		
	29.10 nM	43.18		
	9.09 nM	= 39.91		
	2.84 nM	27.13		

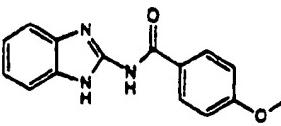
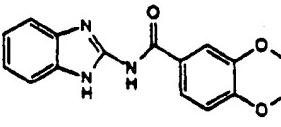
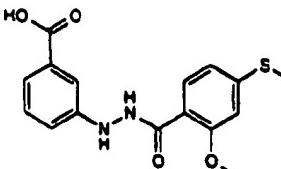
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59-0098				
59-0098	100.00 μM	-1.38		
	31.25 μM	186.89		
	9.77 μM	221.7		
	3.05 μM	164.69		
	953.67 nM	96.94		
	298.02 nM	68.25		
	93.13 nM	57		
	29.10 nM	51.88		
	9.09 nM	41.29		
	2.84 nM	33.43		
				
59-0099				
59-0099	100.00 μM	13.040		
	31.25 μM	56.880		
	9.77 μM	119.340		
	3.05 μM	237.420		
	953.67 nM	285.440		
	298.02 nM	164.610		
	93.13 nM	123.300		
	29.10 nM	69.240		
	9.09 nM	44.500		
	2.84 nM	47.390		
				
59-0100				
59-0100	100.00 μM	-10.020		
	31.25 μM	-10.730		
	9.77 μM	30.340		
	3.05 μM	114.410		
	953.67 nM	77.540		
	298.02 nM	40.280		
	93.13 nM	35.730		
	29.10 nM	28.280		
	9.09 nM	17.480		
	2.84 nM	11.470		
				
59-0101				
59-0101	100.00 μM	26.370		

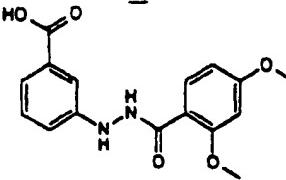
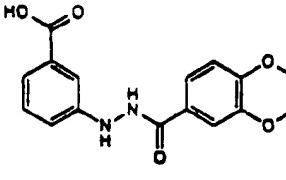
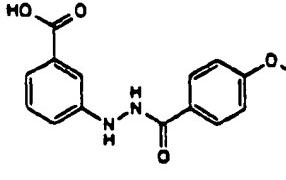
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		31.25 <u>M</u>	12.440
		9.77 <u>M</u>	-0.780
		3.05 <u>M</u>	10.280
		953.67 <u>nM</u>	2.110
		298.02 <u>nM</u>	7.860
		93.13 <u>nM</u>	1.140
		29.10 <u>nM</u>	2.820
		9.09 <u>nM</u>	4.150
		2.84 <u>nM</u>	5.590
			
59-0102	284.34		
		100.00 <u>M</u>	-24.350
		31.25 <u>M</u>	-11.140
		9.77 <u>M</u>	63.540
		3.05 <u>M</u>	121.320
		953.67 <u>nM</u>	79.530
		298.02 <u>nM</u>	72.460
		93.13 <u>nM</u>	66.290
		29.10 <u>nM</u>	45.690
		9.09 <u>nM</u>	27.280
		2.84 <u>nM</u>	42.330
		888.18 <u>pM</u>	33.430
			
59-0103	313.38		
		100.00 <u>M</u>	-29.69
		31.25 <u>M</u>	-29.53
		9.77 <u>M</u>	-28.22
		3.05 <u>M</u>	-27.72
		953.67 <u>nM</u>	-5.58
		298.02 <u>nM</u>	54.15
		93.13 <u>nM</u>	170.95
		29.10 <u>nM</u>	222.87
		9.09 <u>nM</u>	210.39
		2.84 <u>nM</u>	203.4
		0.80 <u>nM</u>	114.55
			
59-0104	297.31		
		100.00 <u>M</u>	-29.84
		31.25 <u>M</u>	-28.72
		9.77 <u>M</u>	-29.2
		3.05 <u>M</u>	-27.05
		953.67 <u>nM</u>	24.37
		298.02 <u>nM</u>	196.42
		93.13 <u>nM</u>	213.89

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		29.10 nM	320.04
		9.09 nM	245.42
		2.84 nM	182.45
		0.80 nM	119.55
<hr/>			
			
59-0105	267.29		
		100.00 μM	-25.72
		31.25 μM	-15.89
		9.77 μM	31.7
		3.05 μM	54.17
		953.67 nM	53.67
		298.02 nM	41.35
		93.13 nM	44.5
		29.10 nM	39.02
		9.09 nM	25.38
		2.84 nM	31.7
		0.80 nM	18.05
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59-0106	287.31		
		100.00 μM	-14.05
		31.25 μM	223.52
		9.77 μM	202.58
		3.05 μM	107.73
		953.67 nM	71.3
		298.02 nM	44.84
		93.13 nM	26.54
		29.10 nM	23.05
		9.09 nM	27.87
		2.84 nM	12.23
		0.80 nM	11.4
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59-0107	332.38		
		100.00 μM	48.55
		31.25 μM	22.87
		9.77 μM	7.19
		3.05 μM	0.65
		953.67 nM	-11.12
		298.02 nM	-3.92
		93.13 nM	1.09
		29.10 nM	-15.69

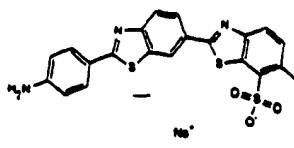
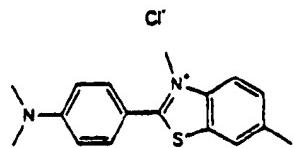
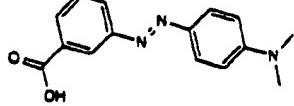
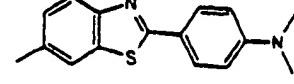
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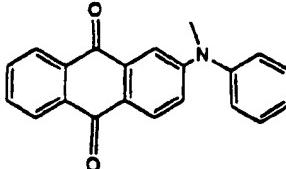
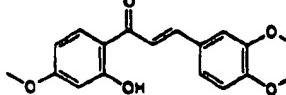
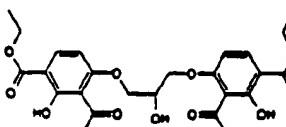
		9.09 nM	-11.32
		2.84 nM	-2.62
		0.80 nM	-16.11
	59-0108	316.31	
		100.00 μM	227.73
		31.25 μM	96.02
		9.77 μM	58.57
		3.05 μM	37.23
		953.67 nM	18.94
		298.02 nM	25.66
		93.13 nM	-4.6
		29.10 nM	2.62
		9.09 nM	-4.6
		2.84 nM	3.92
		0.80 nM	4.14
	59-0109	316.31	
		100.00 μM	43.12
		31.25 μM	27.64
		9.77 μM	5.89
		3.05 μM	6.32
		953.67 nM	13.51
		298.02 nM	7.85
		93.13 nM	3.71
		29.10 nM	-3.27
		9.09 nM	5.01
		2.84 nM	-4.58
		0.80 nM	6.98
	59-0110	286.29	
		100.00 μM	65.11
		31.25 μM	67.05
		9.77 μM	-35.27
		3.05 μM	25.26
		953.67 nM	27.01
		298.02 nM	15.24

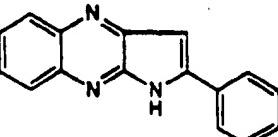
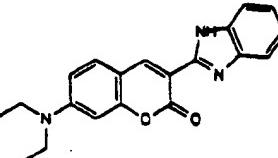
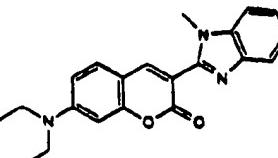
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		93.13nM	29.10nM	9.09nM	2.84nM	0.80nM
<chem>Nc1ccc(C(=O)O)cc1</chem>	59-0111	152.15				
		100.00μM	23.380			
		31.25μM	22.330			
		9.77μM	12.260			
		3.05μM	5.390			
		953.67nM	2.190			
		298.02nM	1.230			
		93.13nM	2.430			
		29.10nM	6.350			
		9.09nM	4.350			
		2.84nM	4.350			
		0.80nM	3.230			
<chem>CN(C)c1ccc(CC=O)cc1</chem>	59-0112	149.19				
		100.00μM	2.670			
		31.25μM	4.670			
		9.77μM	2.790			
		3.05μM	3.790			
		953.67nM	4.270			
		298.02nM	1.150			
		93.13nM	9.630			
		29.10nM	0.620			
		9.09nM	0.510			
		2.84nM	12.800			
		0.80nM	2.990			
<chem>CN(C)c1ccc(cc1Cc2nc3ccccc23)c2ccccc2</chem>	59-0113	274.37				
		100.00μM	22.010			
		31.25μM	25.940			
		9.77μM	7.500			
		3.05μM	3.070			
		953.67nM	-0.780			
		298.02nM	-4.690			
		93.13nM	-4.780			
		29.10nM	5.090			
		9.09nM	0.150			
		2.84nM	-0.250			
		0.80nM	0.150			

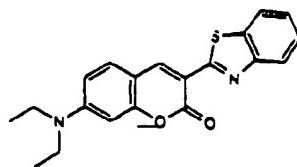
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59-0114	475.54			
	100.00 μM	52.030		
	31.25 μM	36.120		
	9.77 μM	25.840		
	3.05 μM	16.670		
	953.67 nM	12.540		
	298.02 nM	8.420		
	93.13 nM	-1.060		
	29.10 nM	2.160		
	9.09 nM	-6.000		
	2.84 nM	2.470		
	0.80 nM	-1.460		
				
59-0115	318.87			
	100.00 μM	73.700		
	31.25 μM	2.770		
	9.77 μM	-10.430		
	3.05 μM	-12.340		
	953.67 nM	-13.780		
	298.02 nM	-13.960		
	93.13 nM	-11.940		
	29.10 nM	-9.830		
	9.09 nM	-8.820		
	2.84 nM	-0.950		
	0.80 nM	-0.050		
				
59-0116	269.30			
	100.00 μM	31.380		
	31.25 μM	109.060		
	9.77 μM	231.070		
	3.05 μM	240.670		
	953.67 nM	132.020		
	298.02 nM	75.820		
	93.13 nM	53.250		
	29.10 nM	47.500		
	9.09 nM	39.440		
	2.84 nM	42.170		
	0.80 nM	31.180		
				
59-0117	268.38			
	100.00 μM	-68.520		

		31.25 μ M	-57.450
		9.77 μ M	111.630
		3.05 μ M	64.340
		953.67 nM	4.740
		298.02 nM	-19.270
		93.13 nM	-26.660
		29.10 nM	-28.880
		9.09 nM	-42.180
		2.84 nM	-41.300
		0.80 nM	-39.220
			
59-0118	313.38	100.00 μ M	-67.170
		31.25 μ M	-56.580
		9.77 μ M	-58.080
		3.05 μ M	-55.720
		953.67 nM	-48.200
		298.02 nM	-50.300
		93.13 nM	-33.310
		29.10 nM	-47.340
		9.09 nM	-48.310
		2.84 nM	-56.200
		0.80 nM	-57.310
			
59-0119	314.34	100.00 μ M	167.500
		31.25 μ M	-29.240
		9.77 μ M	-57.800
		3.05 μ M	-52.030
		953.67 nM	-54.240
		298.02 nM	-53.870
		93.13 nM	-38.110
		29.10 nM	-55.100
		9.09 nM	-52.270
		2.84 nM	-53.500
		0.80 nM	-43.650
			
59-0120	504.49	100.00 μ M	-62.790
		31.25 μ M	-60.470
		9.77 μ M	-66.600
		3.05 μ M	-60.790
		953.67 nM	-54.240
		298.02 nM	-45.250
		93.13 nM	-50.660

		29.10 nM	-50.300
		9.09 nM	-50.300
		2.84 nM	-50.300
		0.80 nM	-43.280
	59-0121	245.29	
		100.00 μM	-79.890
		31.25 μM	-75.580
		9.77 μM	25.850
		3.05 μM	94.850
		953.67 nM	43.910
		298.02 nM	-1.800
		93.13 nM	-4.150
		29.10 nM	-22.030
		9.09 nM	-31.110
		2.84 nM	-26.760
		0.80 nM	-28.270
	59-0122	333.39	
		100.00 μM	-19.050
		31.25 μM	-12.080
		9.77 μM	-7.610
		3.05 μM	25.210
		953.67 nM	63.580
		298.02 nM	67.220
		93.13 nM	63.890
		29.10 nM	42.680
		9.09 nM	45.320
		2.84 nM	37.780
		0.80 nM	27.030
	59-0123	347.42	
		100.00 μM	34.430
		31.25 μM	34.710
		9.77 μM	38.620
		3.05 μM	55.100
		953.67 nM	51.900
		298.02 nM	41.410
		93.13 nM	29.970
		29.10 nM	-13.760
		9.09 nM	17.120
		2.84 nM	13.480
		0.80 nM	1.190

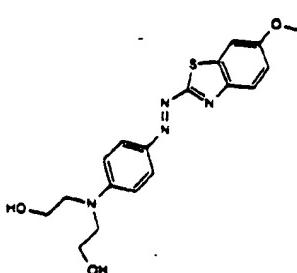
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59-0124

350.44

	100.00 μM	56.640
	31.25 μM	61.500
	9.77 μM	145.880
	3.05 μM	135.830
	953.67 nM	288.990
	298.02 nM	224.290
	93.13 nM	134.850
	29.10 nM	91.690
	9.09 nM	80.390
	2.84 nM	63.060
	0.80 nM	51.460

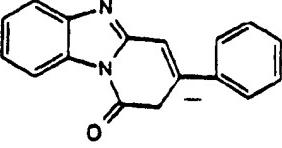
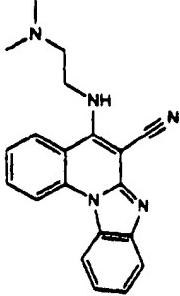
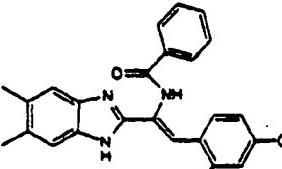


59-0125

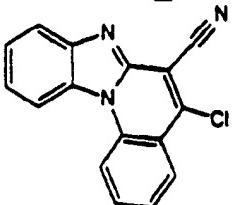
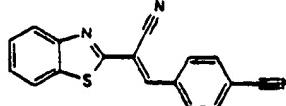
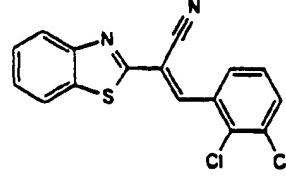
372.45

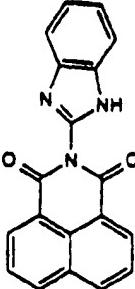
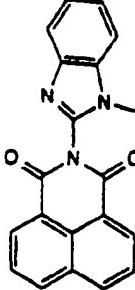
	100.00 μM	-6.780
	31.25 μM	67.530
	9.77 μM	54.120
	3.05 μM	28.700
	953.67 nM	21.980
	298.02 nM	22.280
	93.13 nM	22.700
	29.10 nM	1.630
	9.09 nM	15.700
	2.84 nM	9.840
	0.80 nM	8.460

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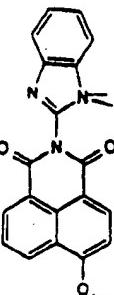
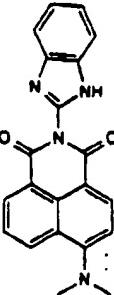
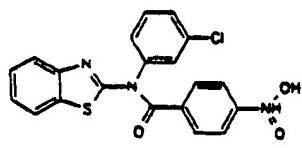
				
59-0126	260.30			
	100.00 μM	-17.390		
	31.25 μM	-13.100		
	9.77 μM	9.270		
	3.05 μM	40.530		
	953.67 nM	21.390		
	298.02 nM	29.660		
	93.13 nM	9.430		
	29.10 nM	6.360		
	9.09 nM	6.510		
	2.84 nM	0.080		
	0.80 nM	3.750		
				
59-0127	329.41			
	100.00 μM	-20.610		
	31.25 μM	-21.820		
	9.77 μM	-6.080		
	3.05 μM	-3.800		
	953.67 nM	-6.820		
	298.02 nM	-6.200		
	93.13 nM	11.880		
	29.10 nM	1.610		
	9.09 nM	3.600		
	2.84 nM	-2.070		
	0.80 nM	4.220		
				
59-0128	436.34			
	100.00 μM			
	31.25 μM			
	9.77 μM			
	3.05 μM			
	953.67 nM			
	298.02 nM			
	93.13 nM			
	29.10 nM			

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		IC ₅₀ nM				
		2.84 nM	0.80 nM			
						
59-0129	277.71					
		100.00 μM	-20.46			
		31.25 μM	-21.21			
		9.77 μM	44.36			
		3.05 μM	4.38			
		953.67 nM	5.91			
		298.02 nM	3.81			
		93.13 nM	2.07			
		29.10 nM	4.22			
		9.09 nM	-0.88			
		2.84 nM	12.48			
		0.80 nM	-0.53			
						
59-0130	287.34					
		100.00 μM	4.38			
		31.25 μM	8.35			
		9.77 μM	5.91			
		3.05 μM	4.98			
		953.67 nM	0.39			
		298.02 nM	8.66			
		93.13 nM	2.65			
		29.10 nM	3.61			
		9.09 nM	4.36			
		2.84 nM	8.96			
		0.80 nM	24.75			
						
59-0131	331.22					
		100.00 μM	8.75			
		31.25 μM	0.12			
		9.77 μM	-10.38			
		3.05 μM	-6.39			
		953.67 nM	-2.81			
		298.02 nM	1.61			
		93.13 nM	-1.98			
		29.10 nM	-2.59			
		9.09 nM	0.14			
		2.84 nM	-5.77			

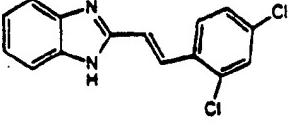
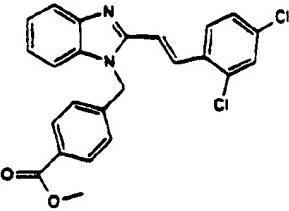
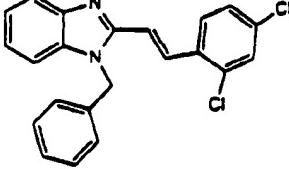
		0.80 nM	-0.51		
					
59-0132	313.32	100.00 μM	-17.11		
		31.25 μM	-14.81		
		9.77 μM	-14.37		
		3.05 μM	-12.92		
		953.67 nM	-13.54		
		298.02 nM	-10.58		
		93.13 nM	-3.65		
		29.10 nM	-7.68		
		9.08 nM	-6.18		
		2.84 nM	-9.97		
		0.80 nM	-2.81		
					
59-0133	327.34	100.00 μM	-16.04		
		31.25 μM	-16.91		
		9.77 μM	-17.31		
		3.05 μM	-16.71		
		953.67 nM	-9.34		
		298.02 nM	-12.69		
		93.13 nM	-11.23		
		29.10 nM	-17.74		
		9.08 nM	6.02		
		2.84 nM	-4.71		
		0.80 nM	0.55		

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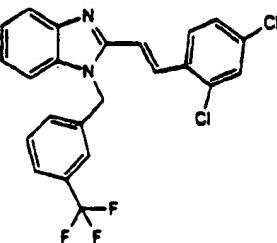
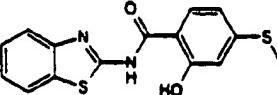
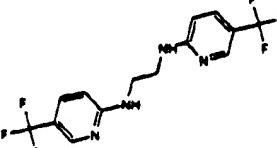
				
59-0134	357.37			
	100.00 μM			
	31.25 μM			
	9.77 μM			
	3.05 μM			
	953.67 nM			
	298.02 nM			
	93.13 nM			
	29.10 nM			
	9.09 nM			
	2.84 nM			
	0.80 nM			
				
59-0135	356.39			
	100.00 μM	-21.3		
	31.25 μM	-14.16		
	9.77 μM	-1.98		
	3.05 μM	0.97		
	953.67 nM	11.68		
	298.02 nM	-1.13		
	93.13 nM	-1.55		
	29.10 nM	-2.81		
	9.09 nM	12.11		
	2.84 nM	-5.75		
	0.80 nM	4.54		
				
59-0136	411.87			
	100.00 μM			
	31.25 μM	+		
	9.77 μM			
	3.05 μM			
	953.67 nM			

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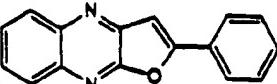
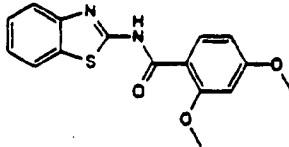
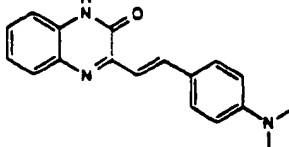
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		29.45 nM	4.84
		9.09 nM	13.93
		2.84 nM	18.61
		0.80 nM	10.05
	59-0140	289.17	
		100.00 μM	
		31.25 μM	
		9.77 μM	
		3.05 μM	
		953.67 nM	
		298.02 nM	
		93.13 nM	
		29.10 nM	
		9.09 nM	
		2.84 nM	
		0.80 nM	
	59-0141	437.33	
		100.00 μM	-8.76
		31.25 μM	5.69
		9.77 μM	19.85
		3.05 μM	43.98
		953.67 nM	44.73
		298.02 nM	37.12
		93.13 nM	24.36
		29.10 nM	18.61
		9.09 nM	26.71
		2.84 nM	15.98
		0.80 nM	7.87
	59-0142	379.29	
		100.00 μM	9.43
		31.25 μM	33.72
		9.77 μM	47.33
		3.05 μM	40.18
		953.67 nM	36.53
		298.02 nM	29.94
		93.13 nM	22.11

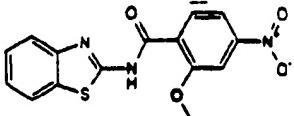
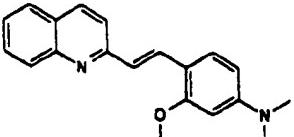
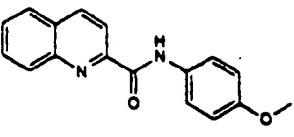
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		52K86 nM	0.91
		0.091nM	19.14!
		2.841nM	10.38!
		0.801nM	17.12!
	59-0143	447.29	
		100.00 μM	0.4!
		31.25 μM	34.39!
		9.77 μM	42.21!
		3.05 μM	50.57!
		953.67 nM	36.94!
		298.02 nM	27.23!
		93.13 nM	16.99!
		29.10 nM	18.27!
		9.09 nM	14.42!
		2.84 nM	11.33!
		0.80 nM	23.72!
	59-0144	318.40	
		100.00 μM	-14.59!
		31.25 μM	-4.44!
		9.77 μM	47.1!
		3.05 μM	53.89!
		953.67 nM	43.11!
		298.02 nM	29.2!
		93.13 nM	18.5!
		29.10 nM	12.9!
		9.09 nM	5.54!
		2.84 nM	3.71!
		0.80 nM	5.87!
	59-0145	350.27	
		100.00 μM	435.91!
		31.25 μM	422.15!
		9.77 μM	446.93!
		3.05 μM	434.17!
		953.67 nM	238.34!
		298.02 nM	45.99!
		93.13 nM	9.22!
		29.10 nM	7.71!
		9.09 nM	0.11!

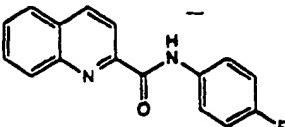
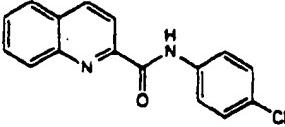
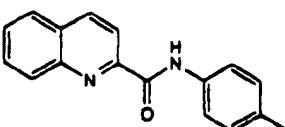
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		2.84nM	6.27i
		0.80nM	3.55i
	59-0146	246.27	
		100.00i <u>M</u>	-63.05i
		31.25i <u>M</u>	4.42i
		9.77i <u>M</u>	-13.73i
		3.05i <u>M</u>	-16.45i
		953.67i <u>M</u>	-35.47i
		298.02i <u>M</u>	-51.25i
		93.13i <u>M</u>	-50.13i
		29.10i <u>M</u>	-42.92i
		9.09i <u>M</u>	-45.64i
		2.84i <u>M</u>	-56.58i
		0.80i <u>M</u>	-39.68i
	59-0147	314.36	
		100.00i <u>M</u>	-85i
		31.25i <u>M</u>	-85i
		9.77i <u>M</u>	-80.29i
		3.05i <u>M</u>	-41.67i
		953.67i <u>M</u>	78.69i
		298.02i <u>M</u>	269.13i
		93.13i <u>M</u>	323.59i
		29.10i <u>M</u>	339.88i
		9.09i <u>M</u>	270.48i
		2.84i <u>M</u>	245.58i
		0.80i <u>M</u>	180.33i
	59-0148	291.35	
		100.00i <u>M</u>	-68.38i
		31.25i <u>M</u>	-36.33i
		9.77i <u>M</u>	-2.3i
		3.05i <u>M</u>	12.12i
		953.67i <u>M</u>	-2.42i
		298.02i <u>M</u>	-16.21i
		93.13i <u>M</u>	-30.87i
		29.10i <u>M</u>	-35.98i
		9.09i <u>M</u>	-39.07i
		2.84i <u>M</u>	-41.18i
		0.80i <u>M</u>	-45.53i

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59-0149	329.33				
	100.00 μM	-16.9			
	31.25 μM	-1.8			
	9.77 μM	-0.53			
	3.05 μM	15.29			
	953.67 nM	78.78			
	298.02 nM	183.5			
	93.13 nM	223.57			
	29.10 nM	173.93			
	9.09 nM	122.3			
	2.84 nM	98.02			
	0.80 nM	69.06			
					
59-0150	304.39				
	100.00 μM	63.32			
	31.25 μM	103.53			
	9.77 μM	416.26			
	3.05 μM	497.21			
	953.67 nM	298.19			
	298.02 nM	193.35			
	93.13 nM	99.48			
	29.10 nM	69.96			
	9.09 nM	59			
	2.84 nM	52.18			
	0.80 nM	48.75			
					
59-0151	278.31				
	100.00 μM	-6.660			
	31.25 μM	18.240			
	9.77 μM	18.300			
	3.05 μM	11.890			
	953.67 nM	8.500			
	298.02 nM	9.070			
	93.13 nM	6.110			
	29.10 nM	5.880			
	9.09 nM	7.700			
	2.84 nM	2.000			
	0.80 nM	1.210			

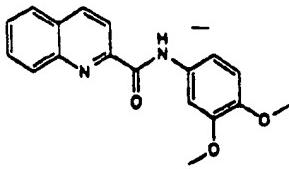
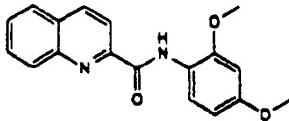
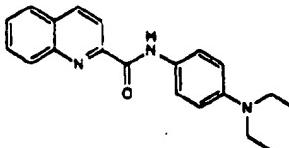
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59-0152	266.275					
		100.00 μM	-6.890			
		31.25 μM	12.490			
		9.77 μM	21.950			
		3.05 μM	12.820			
		953.67 nM	7.350			
		298.02 nM	4.290			
		93.13 nM	9.750			
		29.10 nM	4.660			
		9.09 nM	1.320			
		2.84 nM	4.280			
		0.80 nM	4.160			
						
59-0153	282.73					
		100.00 μM	-4.150			
		31.25 μM	-0.390			
		9.77 μM	11.120			
		3.05 μM	14.540			
		953.67 nM	9.520			
		298.02 nM	11.570			
		93.13 nM	-0.160			
		29.10 nM	1.550			
		9.09 nM	-0.960			
		2.84 nM	4.730			
		0.80 nM	5.650			
						
59-0154	262.312					
		100.00 μM	0.290			
		31.25 μM	24.670			
		9.77 μM	15.680			
		3.05 μM	14.540			
		953.67 nM	13.170			
		298.02 nM	5.840			
		93.13 nM	2.690			
		29.10 nM	-1.190			
		9.09 nM	2.460			
		2.84 nM	4.170			
		0.80 nM	1.890			

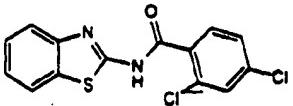
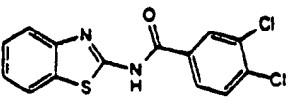
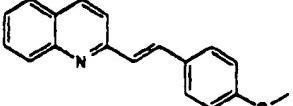
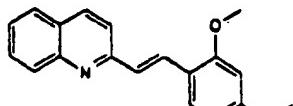
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59-0155	316.282				
59-0155	100.00 μM	-2.950			
	31.25 μM	1.900			
	9.77 μM	-9.450			
	3.05 μM	-0.220			
	953.67 nM	0.690			
	298.02 nM	5.090			
	93.13 nM	-3.250			
	29.10 nM	0.530			
	9.09 nM	-1.900			
	2.84 nM	9.480			
	0.80 nM	-1.130			
59-0156	333.391				
59-0156	100.00 μM	5.840			
	31.25 μM	2.050			
	9.77 μM	7.980			
	3.05 μM	6.690			
	953.67 nM	-0.370			
	298.02 nM	-1.680			
	93.13 nM	-3.550			
	29.10 nM	-7.340			
	9.09 nM	-1.590			
	2.84 nM	2.650			
	0.80 nM	2.500			
59-0157	290.366				
59-0157	100.00 μM	-6.440			
	31.25 μM	14.920			
	9.77 μM	19.930			
	3.05 μM	11.440			
	953.67 nM	8.570			
	298.02 nM	-7.190			
	93.13 nM	0.080			
	29.10 nM	-0.230			
	9.09 nM	-4.460			
	2.84 nM	2.200			
	0.80 nM	9.920			

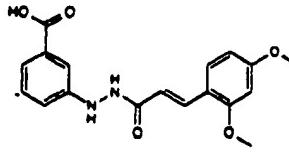
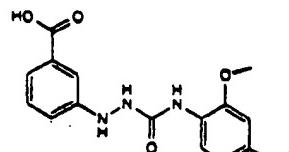
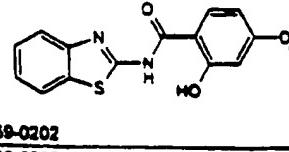
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59-0158	308.337				
59-0158	100.00 μM	-5.980			
	31.25 μM	3.720			
	9.77 μM	16.140			
	3.05 μM	27.080			
	953.67 nM	9.930			
	298.02 nM	11.900			
	93.13 nM	2.810			
	29.10 nM	3.110			
	9.09 nM	0.690			
	2.84 nM	1.900			
	0.80 nM	7.970			
					
59-0159	308.337				
59-0159	100.00 μM	2.790			
	31.25 μM	13.530			
	9.77 μM	4.700			
	3.05 μM	10.910			
	953.67 nM	2.800			
	298.02 nM	9.710			
	93.13 nM	4.830			
	29.10 nM	0.650			
	9.09 nM	5.900			
	2.84 nM	6.610			
	0.80 nM	6.250			
					
59-0160	319.408				
59-0160	100.00 μM	-5.080			
	31.25 μM	-3.390			
	9.77 μM	5.300			
	3.05 μM	15.910			
	953.67 nM	6.610			
	298.02 nM	11.380			
	93.13 nM	4.460			
	29.10 nM	3.520			
	9.09 nM	4.700			
	2.84 nM	-0.650			
	0.80 nM	7.560			

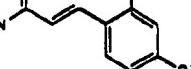
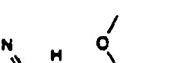
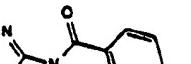
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59-0196	323.201				
59-0196	100.00 μM				
	31.25 μM				
	9.77 μM				
	3.05 μM				
	953.67 nM				
	298.02 nM				
	93.13 nM				
	29.10 nM				
	9.09 nM				
	2.84 nM				
	0.80 nM				
					
59-0197	323.201				
59-0197	100.00 μM				
	31.25 μM				
	9.77 μM				
	3.05 μM				
	953.67 nM				
	298.02 nM				
	93.13 nM				
	29.10 nM				
	9.09 nM				
	2.84 nM				
	0.80 nM				
					
59-0198	281.324				
59-0198	100.00 μM				
	31.25 μM				
	9.77 μM				
	3.05 μM				
	953.67 nM				
	298.02 nM				
	93.13 nM				
	29.10 nM				
	9.09 nM				
	2.84 nM				
	0.80 nM				
					
59-0199	291.35				
59-0199	100.00 μM				
	31.25 μM				

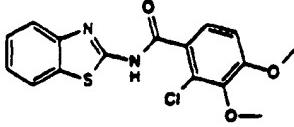
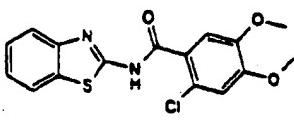
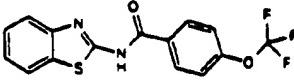
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		4.00 μ M
		3.05 μ M
		953.67 nM
		298.02 nM
		93.13 nM
		29.10 nM
		9.09 nM
		2.84 nM
		0.80 nM
	59-0200	342.351
	59-0200	100.00 μ M
		31.25 μ M
		9.77 μ M
		3.05 μ M
		953.67 nM
		298.02 nM
		93.13 nM
		29.10 nM
		9.09 nM
		2.84 nM
		0.80 nM
	59-0201	331.328
	59-0201	100.00 μ M
		31.25 μ M
		9.77 μ M
		3.05 μ M
		953.67 nM
		298.02 nM
		93.13 nM
		29.10 nM
		9.09 nM
		2.84 nM
		0.80 nM
	59-0202	300.336
	59-0202	100.00 μ M
		31.25 μ M
		9.77 μ M
		3.05 μ M
		953.67 nM
		298.02 nM
		93.13 nM
		29.10 nM

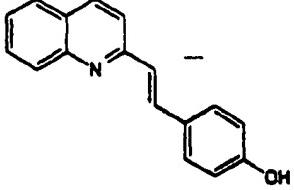
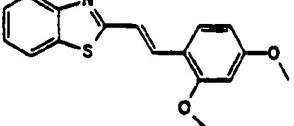
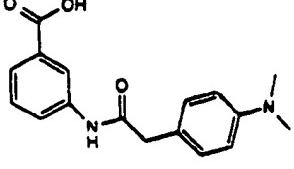
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		9.09 nM			
		2.84 nM			
		0.80 nM			
<hr/>					
					
59-0203	292.338				
59-0203		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
<hr/>					
					
59-0204	344.389				
59-0204		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
<hr/>					
					
59-0205	318.782				
59-0205		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			

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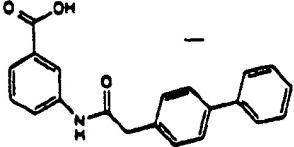
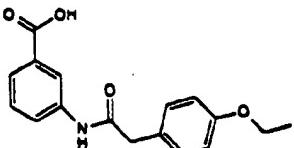
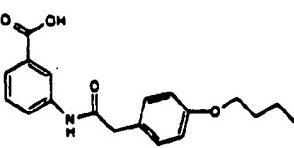
						
59-0206	348.808					
59-0206		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0207	348.808					
59-0207		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-0208	338.307					
59-0208		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				

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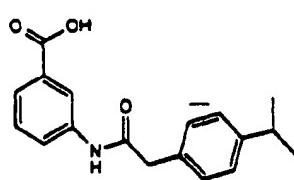
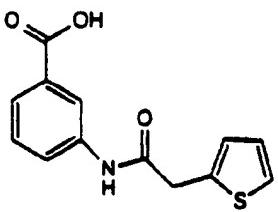
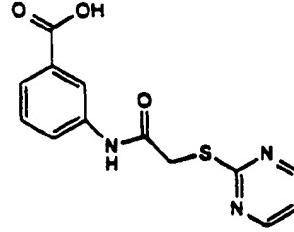
						
59-0209	247.297					
59-0209	100.00 μM					
	31.25 μM					
	9.77 μM					
	3.05 μM					
	953.67 nM					
	298.02 nM					
	93.13 nM					
	29.10 nM					
	9.09 nM					
	2.84 nM					
	0.80 nM					
						
59-0210	297.376					
59-0210	100.00 μM					
	31.25 μM					
	9.77 μM					
	3.05 μM					
	953.67 nM					
	298.02 nM					
	93.13 nM					
	29.10 nM					
	9.09 nM					
	2.84 nM					
	0.80 nM					
						
59-8000	298.342					
59-8000	100.00 μM					
	31.25 μM					
	9.77 μM					
	3.05 μM					
	953.67 nM					
	298.02 nM					
	93.13 nM					
	29.10 nM					
	9.09 nM					
	2.84 nM					
	0.80 nM					

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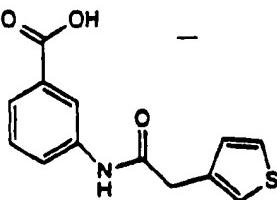
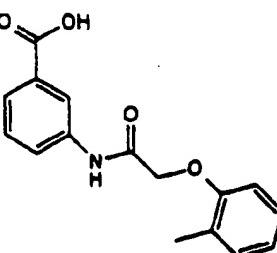
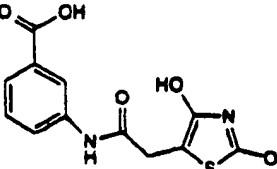
	59-8001	255.273						
59-8001		100.00 μM						
		31.25 μM						
		9.77 μM						
		3.05 μM						
		953.67 nM						
		298.02 nM						
		93.13 nM						
		29.10 nM						
		9.09 nM						
		2.84 nM						
		0.80 nM						
	59-8002	302.286						
59-8002		100.00 μM						
		31.25 μM						
		9.77 μM						
		3.05 μM						
		953.67 nM						
		298.02 nM						
		93.13 nM						
		29.10 nM						
		9.09 nM						
		2.84 nM						
		0.80 nM						
	59-8003	270.288						
59-8003		100.00 μM						
		31.25 μM						
		9.77 μM						
		3.05 μM						
		953.67 nM						
		298.02 nM						
		93.13 nM						
		29.10 nM						
		9.09 nM						
		2.84 nM						
		0.80 nM						

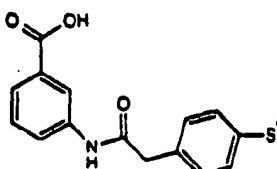
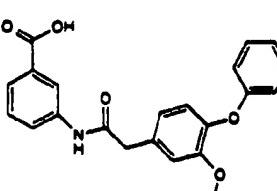
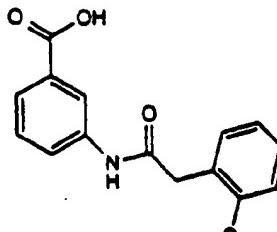
						
59-8004	331.371					
59-8004		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8005	299.326					
59-8005		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8006	327.38					
59-8006		100.00 μM				
		31.25 μM				
		9.77 μM				
		3.05 μM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				

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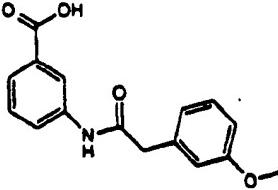
					
59-8007	297.354				
59-8007		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-8008	261.299				
59-8008		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			
		2.84 nM			
		0.80 nM			
					
59-8009	289.313				
59-8009		100.00 μM			
		31.25 μM			
		9.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		9.09 nM			

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		250 nM	0.80 nM				
							
59-8010	281.299						
59-8010		100.00 μM					
		31.25 μM					
		9.77 μM					
		3.05 μM					
		953.67 nM					
		298.02 nM					
		93.13 nM					
		29.10 nM					
		9.09 nM					
		2.84 nM					
		0.80 nM					
							
59-8011	285.299						
59-8011		100.00 μM					
		31.25 μM					
		9.77 μM					
		3.05 μM					
		953.67 nM					
		298.02 nM					
		93.13 nM					
		29.10 nM					
		9.09 nM					
		2.84 nM					
		0.80 nM					
							
59-8012	294.285						
59-8012		100.00 μM					
		31.25 μM					
		9.77 μM					
		3.05 μM					
		953.67 nM					
		298.02 nM					

		50XLS nM			
		29.10 nM			
		8.09 nM			
		2.84 nM			
		0.80 nM			
<hr/>					
					
59-8013	301.364				
59-8013		100.00 μM			
		31.25 μM			
		8.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		8.09 nM			
		2.84 nM			
		0.80 nM			
<hr/>					
					
59-8014	377.396				
59-8014		100.00 μM			
		31.25 μM			
		8.77 μM			
		3.05 μM			
		953.67 nM			
		298.02 nM			
		93.13 nM			
		29.10 nM			
		8.09 nM			
		2.84 nM			
		0.80 nM			
<hr/>					
					
59-8015	285.299				
59-8015		100.00 μM			
		31.25 μM			
		8.77 μM			
		3.05 μM			

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		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				
						
59-8018	285.299					
59-8018		100.00 uM				
		31.25 uM				
		9.77 uM				
		3.05 uM				
		953.67 nM				
		298.02 nM				
		93.13 nM				
		29.10 nM				
		9.09 nM				
		2.84 nM				
		0.80 nM				

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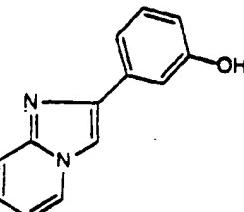
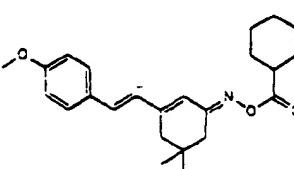
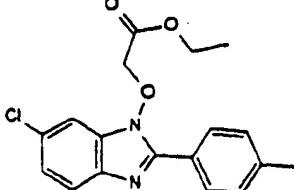
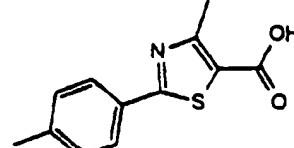
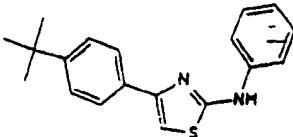
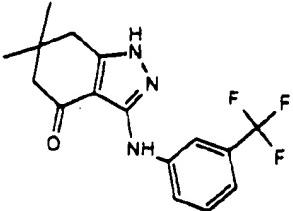
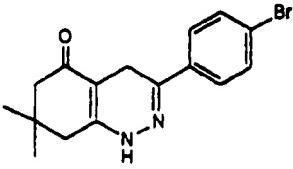
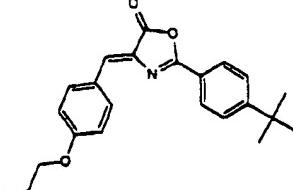
CHEMISTRY	Concentration	ABA-S
		
51-2229		
51-2229	100.00 μM	125.320
	10.00	28.260
210.236	2.00	20.140
	0.40	-9.740
	0.08	-9.710
		
92-3052		
92-3052	131.056 μM	-9.28
	13.108	113.80
381.516	2.621	12.61
	0.524	20.25
	0.105	24.45
		
92-3380		
92-3380	145.012 μM	-8.05
	14.501	31.57
344.798	2.900	139.88
	0.580	49.82
	0.116	21.01
		
92-3552		
92-3552	214.326 μM	108.15

Figure 4

4-L

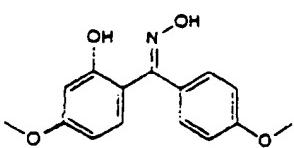
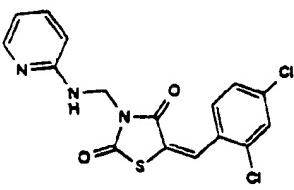
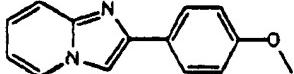
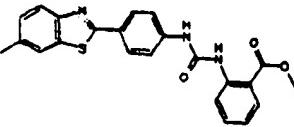
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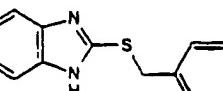
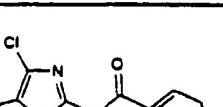
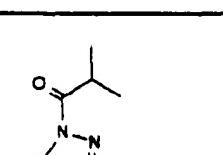
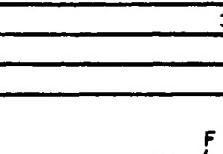
		
92-8258		
92-8258	162.102	μM
	32.420	
308.447	16.210	
	3.242	
	1.621	
	0.324	
		
92-8362		
92-8362	154.647	μM
	30.929	
323.318	15.465	
	3.093	
	1.546	
	0.309	
		
92-8372		
92-8372	150.045	μM
	30.009	
333.234	15.004	
	3.001	
	1.500	
	0.300	
		
92-9183		

	-16.65	
	157.44	
	101.04	
	39.02	
	12.78	
	136.79	
	137.09	
	65.02	
	17.34	
	0.41	
	63.76	
	134.71	
	92.08	
	31.35	
	13.20	

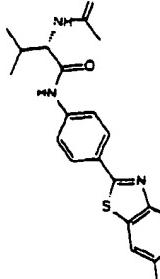
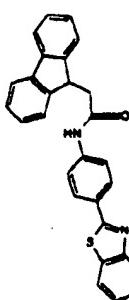
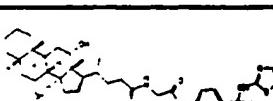
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92-9183		137.568 μM	-22.80
		13.757	16.61
363.457		2.751	101.96
		1.376	
		0.550	58.17
		0.110	38.47
			
93-0215			
93-0215		182.957 μM	115.230
		18.296	88.110
273.288		3.659	20.870
		0.732	-28.680
		0.146	5.250
			
93-0399			
93-0399		131.491 μM	128.130
		13.149	38.580
360.253		2.630	41.240
		0.526	-4.910
		0.105	3.910
			
93-0587			
93-0587		222.953 μM	178.130
		22.295	60.410
224.263		4.458	-0.180
		0.862	3.470
		0.178	-8.460
			
93-1327			
93-1327		119.764 μM	-42.000
		11.976	119.130
417.487		2.385	67.930
		0.479	6.520

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		0.096		
				
93-1340				
93-1340		196.576 μM		
		19.658		
		254.355	3.932	
		0.786		
		0.157		
				
93-1474				
93-1474		145.940 μM		
		14.594		
		342.607	2.919	
		0.584		
		0.117		
				
93-1766				
93-1766		144.348 μM		
		14.435		
		346.396	2.887	
		0.577		
		0.115		
				
93-1866				
93-1866		148.214 μM		
		14.821		
				14.870
				-31.290
				127.340
				35.710
				37.630
				7.280
				-45.110
				110.290
				35.080
				109.040
				40.130

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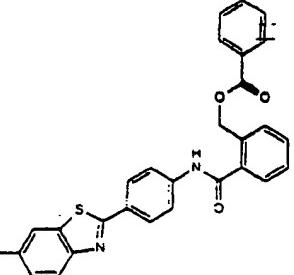
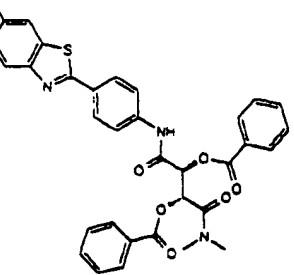
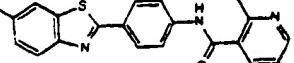
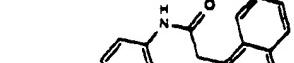
	337.340	2.964	2.800
	--	0.593	-7.360
		0.119	-25.160
			
850-7377			
850-7377		131.062 uM	-50.32
		13.106	68.27
	381.488	2.621	116.61
		0.524	61.26
		0.105	35.86
			
850-7413			
850-7413		111.964 uM	-40.44
		11.196	-2.55
	446.572	2.239	157.01
		0.448	78.73
		0.080	23.97
			
850-7449			
850-7449		69.938 uM	-42.44
		6.994	73.75
	714.923	1.399	112.10
		0.280	75.24
		0.058	28.32

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850-7485		
850-7485	143.099 μM	
	14.310	
349.409	2.862	
	0.572	
	0.114	
850-7991		
850-7991	127.387 μM	
	12.737	
392.565	2.547	
	0.509	
	0.102	
850-8170		
850-8170	101.513 μM	
	10.151	
492.55	2.030	
	0.406	
	0.081	

	-42.91	
	28.36	
	153.04	
	74.27	
	50.28	
	-16.87	
	8.95	
	105.51	
	47.53	
	54.26	
	>	
	-33.79	
	158.65	
	128.27	
	43.05	
	50.00	

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850-8205			
850-8205	104.478 uM		-39.52
	10.448		51.18
	478.57	2.080	163.82
		0.418	108.06
		0.084	73.88
CHIRAL			
			
850-8241			
850-8241	82.279 uM		-2.07
	8.228		181.77
	607.685	1.648	118.23
		0.329	66.73
		0.086	38.14
			
850-8278			
850-8278	139.101 uM		-40.09
	13.910		39.00
	359.461	2.782	182.39
		0.556	122.84
		0.111	78.80
			
850-8387			

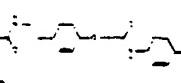
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850-8387		122.392	uM	-17.06
		12.239		130.31
	708.523	2.448		129.75
		0.480		62.69
		0.098		40.74
850-8459				
850-8459		87.921	uM	-21.13
		8.792		11.30
	568.692	1.758		131.92
		0.352		71.13
		0.070		58.55
850-8613				
850-8613		151.319	uM	-26.05
		15.132		85.55
	330.428	3.028		381.37
		0.605		255.32
		0.121		122.93
850-8637				
850-8637		85.518	uM	-25.17
		8.552		33.35
	584.673	1.710		122.49
		0.342		57.19
		0.088		37.42

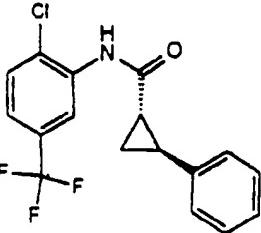
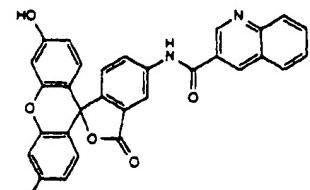
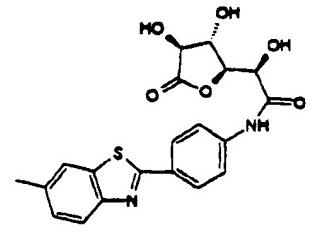
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850-8889			
850-8889	111.493 μM	-17.470	
	11.149	142.970	
	448.457	74.150	
	2.230	21.010	
	0.446	8.530	
	0.089		
850-8964			
850-8964	95.150 μM	-30.92	
	9.516	44.99	
	525.454	126.29	
	1.903	49.84	
	0.381	44.99	
	0.078		
850-9071			
850-9071	109.960 μM	-24.620	
	11.000	64.120	
	454.552	149.030	
	2.200	54.540	
	0.440		

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		0.068	23.540
	850-9106		
850-9106		100.000 μM	-15.710
		10.000	99.820
	499.999	2.000	111.960
		0.400	74.500
		0.060	23.150
	850-9142		
850-9142		85.596 μM	-14.980
		8.560	165.770
	584.138	1.712	66.860
		0.342	27.780
		0.068	0.670
	850-9179		
850-9179		105.357 μM	-24.630
		10.536	105.200
	474.579	2.107	89.280
		0.421	46.110
		0.064	19.180
	850-9212		
850-9212		92.139 μM	-26.580
		9.214	40.900
	542.657	1.843	111.960
		0.389	76.950
		0.074	30.840

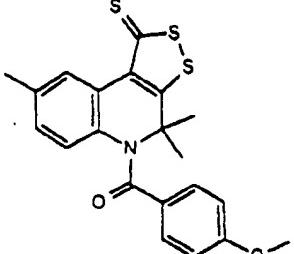
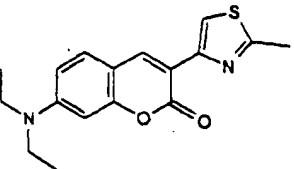
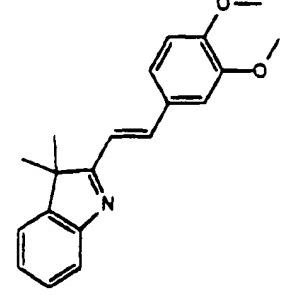
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850-9287		
850-9287	147.170 μM	-15.82
	14.717	15.82
	339.744	130.71
	0.589	91.11
	0.118	69.05
		
850-9356		
850-9356	99.506 μM	-24.650
	9.951	83.140
	502.482	168.810
	0.398	45.470
	0.080	9.740
		
850-9467		
850-9467	120.646 μM	-19.800
	12.085	112.980
	414.438	122.730
	0.483	43.520
	0.097	33.140

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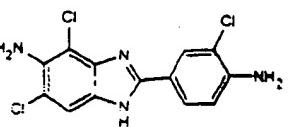
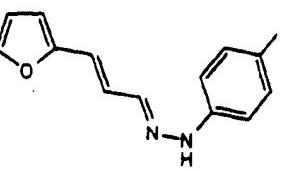
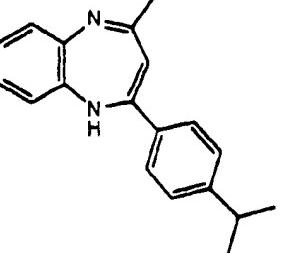
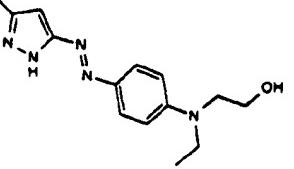
850-9576			
850-9576	111.724	μM	-27.430
	11.172		90.560
	447.532	2.234	101.610
		0.447	44.900
		0.089	19.930
895-0262			
895-0262	168.019	μM	-19.18
	33.204		-12.80
	301.169	16.602	148.28
		3.320	-2.23
		0.332	-3.07
895-0268			
895-0268	128.383	μM	-18.87
	25.577		40.25
	369.458	12.638	169.98
		2.588	165.29
		0.257	14.02

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895-0864		
895-0864	120.896 μM	
	12.090	
	413.58	2.418
		0.484
		0.097
		
895-0867		
895-0867	159.028 μM	
	15.903	
	314.407	3.181
		0.636
		0.127
		
895-0984		
895-0984	182.655 μM	
	16.265	
	307.393	3.253
		0.651
		0.130

	-21.63	
	25.89	
	122.10	
	75.32	
	39.42	
	-30.48	
	148.74	
	74.54	
	25.82	
	3.68	
	-31.08	
	325.06	
	87.51	
	40.39	
	16.03	

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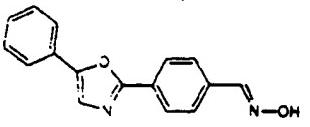
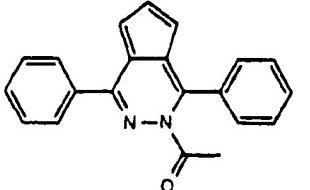
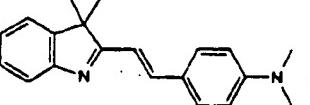
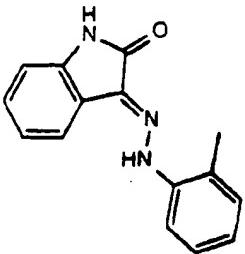
		
895-1161		
895-1161	152.625	uM
	15.263	
327.602	3.053	
	0.611	
	0.122	
		
895-1420		
895-1420	220.965	uM
	22.097	
226.279	4.419	
	0.884	
	0.177	
		
895-1679		
895-1679	180.910	uM
	18.091	
276.383	3.818	
	0.724	
	0.145	
		
895-1691		
895-1691	182.922	uM
	18.292	
273.34	3.658	

	5.51	
	109.31	
	56.08	
	29.49	
	24.71	
	-19.47	
	110.90	
	49.94	
	33.65	
	20.08	
	-30.38	
	111.72	
	102.83	
	18.01	
	0.44	
	-18.29	
	50.84	
	105.70	

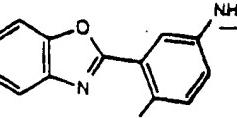
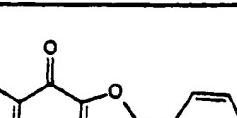
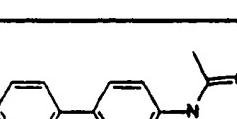
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60.23
23.42
-31.44
132.78
75.39
39.30
16.19
-33.85
29.75
148.84
73.77
28.14
-20.74
128.89
68.37
43.27
19.44
265.41
267.86
227.34
65.40
28.96

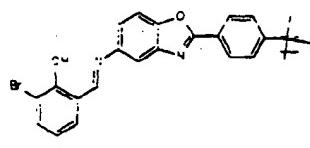
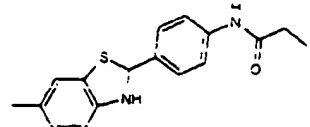
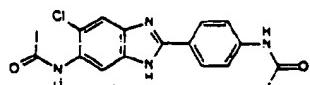
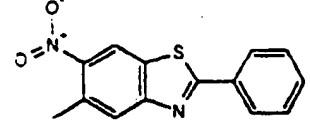
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895-2544			
895-2544	189.186 uM		17.53
	18.919		136.50
254.284	3.784		59.15
	0.757		24.75
	0.151		11.86
			
895-3113			
895-3113	160.067 uM		-22.22
	16.007		224.52
312.372	3.201		68.48
	0.640		43.36
	0.128		30.56
			
895-3306			
895-3306	172.170 uM		-23.24
	17.217		38.83
290.41	3.443		330.10
	0.689		164.63
	0.138		64.33
			
895-3810			
895-3810	198.973 uM		89.79
	19.897		106.75
251.289	3.979		73.78
	0.796		33.45
	0.159		16.86

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895-3846		
895-3846	193.267	uM
	19.327	
258.708	3.865	
	0.773	
	0.155	
		
895-4642		
895-4642	176.473	uM
	17.647	
283.331	3.529	
	0.706	
	0.141	
		
895-4843		
895-4843	159.581	uM
	15.958	
313.312	3.192	
	0.638	
	0.128	
		
895-5185		
895-5185	182.433	uM
	18.243	
307.821	3.249	
	0.650	
	0.130	

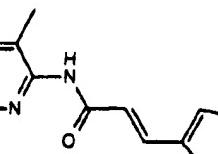
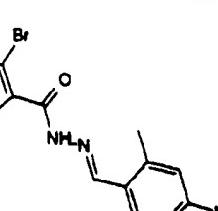
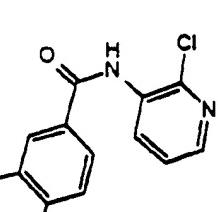
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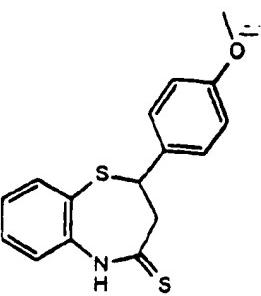
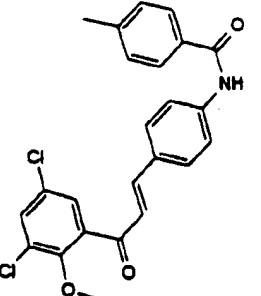
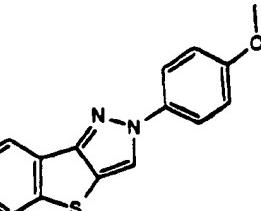
		
895-5960		
	103.348	μM
	10.335	
483.798	2.067	
	0.413	
	0.083	
		
895-5353		
	167.555	μM
	16.755	
298.408	3.351	
	0.670	
	0.134	
		
895-6643		
	145.862	μM
	14.586	
342.786	2.917	
	0.583	
	0.117	
		
895-7828		
	184.973	μM
	18.497	
270.31	3.689	
	0.740	
	0.146	

	-10.03	
	158.04	
	62.07	
	34.47	
	7.24	
	-10.45	
	21.59	
	101.77	
	54.91	
	24.15	
	100.09	
	74.25	
	16.86	
	-0.89	
	-7.94	
	32.44	
	-29.24	
	85.15	
	125.64	
	-30.80	

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		16.933	
295.288		3.387	
		0.677	
		0.135	
			
895-8185			
895-8185		219.057 μM	
		21.906	
	228.251	4.381	
		0.876	
		0.175	
			
895-8286			142.210
895-8286		142.785 μM	40.380
		14.277	17.850
	350.225	2.855	-10.890
		0.571	6.580
		0.114	
			
895-8383			
895-8383		191.774 μM	-44.020
		19.177	78.480
	260.724	3.835	135.940
		0.787	77.030
		0.153	37.630

			
895-8862			
895-8862	165.876	μM	54.72
	16.588		159.21
	301.43	3.318	113.97
		0.664	41.96
		0.133	38.28
			
895-8863			
895-8863	113.552	μM	-20.67
	11.355		201.56
	440.326	2.271	12.95
		0.454	0.62
		0.091	-0.09
			
895-8898			
895-8898	178.349	μM	-29.16
	17.835		0.62
	280.349	3.567	182.84
		0.713	116.55
		0.143	42.75

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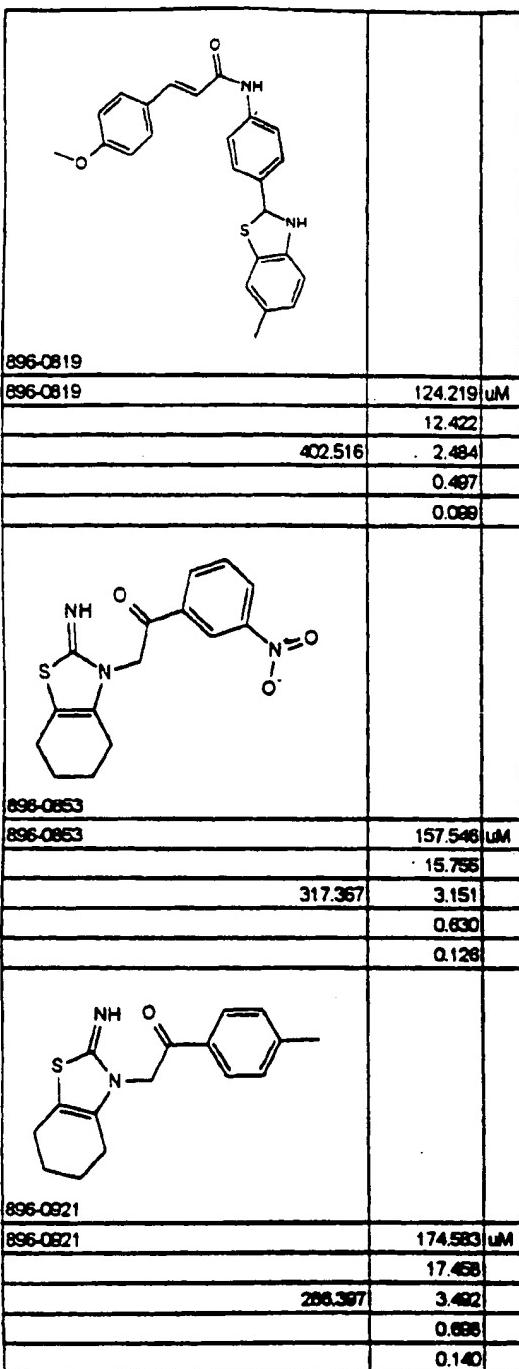
896-0122			
896-0122	190.610	μM	-14.15
	19.081		151.42
262.316	3.812		56.80
	0.762		19.20
	0.152		11.42
896-0246			
896-0246	154.888	μM	-17.57
	15.489		34.35
322.814	3.088		102.03
	0.620		46.52
	0.124		20.52
896-0255			
896-0255	123.000	μM	-17.14
	12.300		67.75
408.504	2.480		168.78
	0.482		61.27
	0.088		49.97
896-0346			
896-0346	107.532	μM	-18.86
	10.753		77.80

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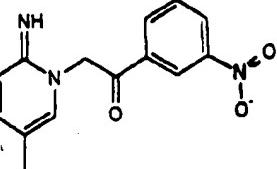
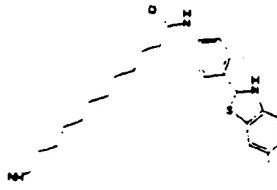
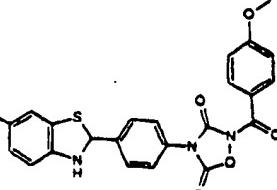
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<chem>Clc1ccc(CC(=O)N2C=CC=C2)cc1</chem>			
896-0686			
896-0686	191.774	uM	-19.80
	19.177		176.04
	260.724	3.835	115.02
		0.767	97.67
		0.153	25.27
<chem>CC(=O)Nc1ccc(cc1)-c2c(c3ccccc3)sc2</chem>			
896-0692			
896-0692	131.269	uM	22.78
	13.127		148.23
	380.697	2.825	78.33
		0.525	51.08
		0.105	46.12
<chem>CCCCCc1ccc(cc1)-c2c(c3ccccc3)sc2</chem>			
896-0719			
896-0719	91.950	uM	-6.49
	9.165		187.43
	543.774	1.839	127.43
		0.368	50.04
		0.074	36.16
<chem>CN1C=CC2=C(Cl)C=C(C=C2)C(=O)N1c3ccccc3</chem>			
896-0773			
896-0773	147.228	uM	-13.94
	14.723		175.33
	339.609	2.945	221.91
		0.509	52.46
		0.118	32.99

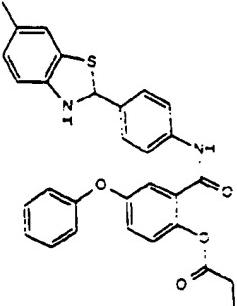
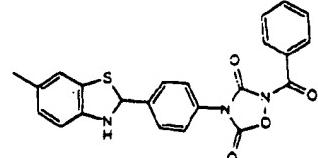
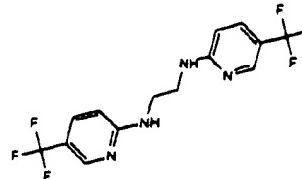
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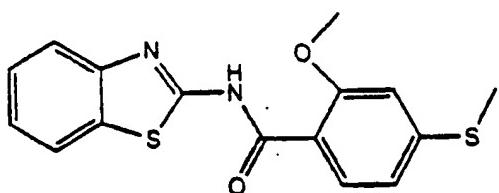
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896-0936		
896-0936	184.314	μM
	18.431	
271.276	3.688	
	0.737	
	0.147	
		
896-0959		
896-0959	103.798	μM
	10.380	
481.703	2.078	
	0.415	
	0.083	
		
896-1201		
896-1201	108.343	μM
	10.634	
481.496	2.167	
	0.433	
	0.087	

	-16.20	
	153.61	
	184.53	
	79.16	
	32.61	
	-1.73	
	102.48	
	61.61	
	63.58	
	48.27	
	-45.70	
	92.57	
	191.83	
	47.22	
	58.25	

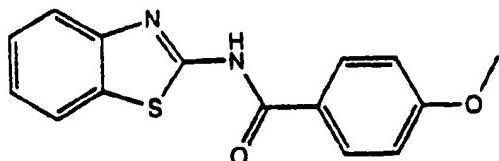
			
896-1301			
896-1301	97.922 uM		-24.32
	9.792		102.49
510.612	1.958		139.28
	0.392		97.89
	0.078		23.45
			
896-1349			
896-1349	115.883 uM		-39.92
	11.588		55.08
431.47	2.318		122.68
	0.464		67.25
	0.083		3.39
			
896-1362			
896-1362	142.749 uM		1.073.91
	14.275		1.082.17
350.206	2.855		884.71
	0.571		-9.82
	0.114		-20.37

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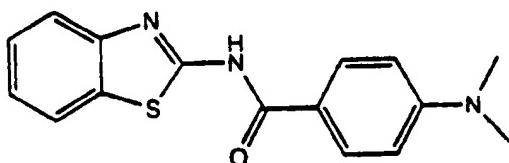
Max : 215 %
EC50 : < 0.8 nM

59-0072



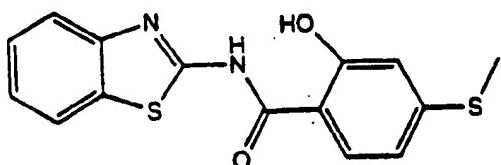
Max : 121 %
EC50 : 30 nM

59-0102



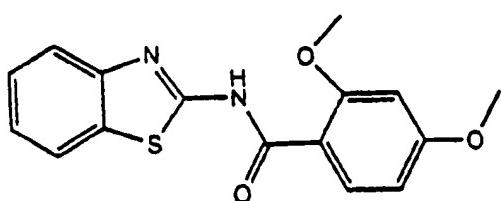
Max : 214 %
EC50 : 200 nM

59-0070



Max : 54 %
EC50 : 2 μM

59-0144

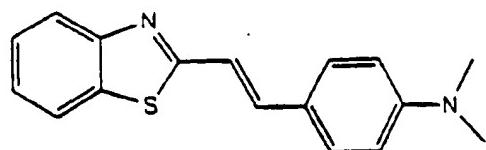


Max : 340 %
EC50 : < 0.8 nM

59-0147

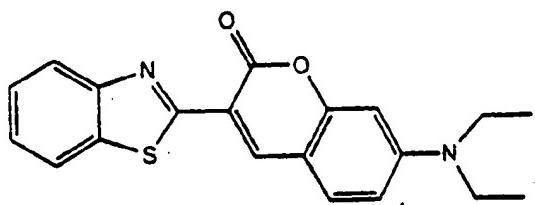
FIG. 5A

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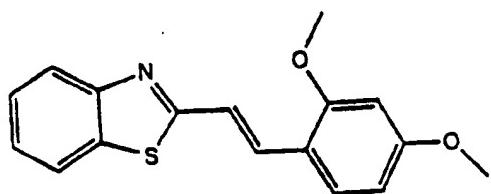


Max : 285 %
EC50 : 3 nM

59-0099



Max : 269 %
EC50 : < 0.8 nM

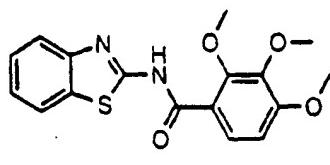


Max : 200 %
EC50 : 30 nM

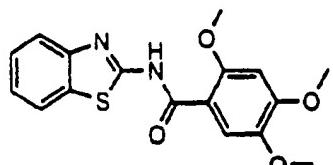
59-0210

5B
FIG.

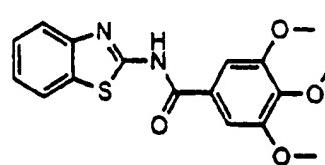
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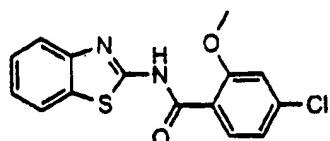
Max : 155 %
EC50 : 20 nM



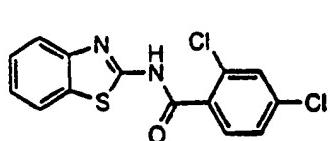
Max : 95 %
EC50 : 30 nM



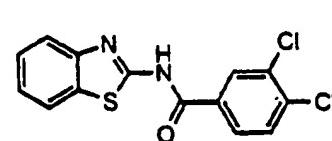
Inactive



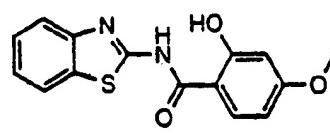
Max : 155 %
EC50 : 20 nM



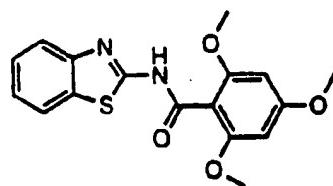
Inactive



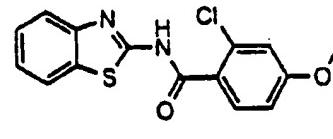
Max : 162 %
EC50 : 150 nM



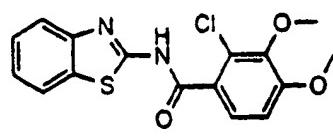
Max : 155 %
EC50 : 150 nM



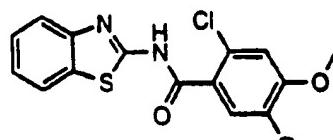
Max : 70 %
EC50 : 50 nM



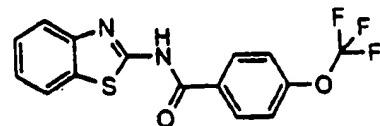
Max : 250 %
EC50 : < 0.8 nM



Max : 150 %
EC50 : 20 nM



Max : 50 %
EC50 : 100 nM

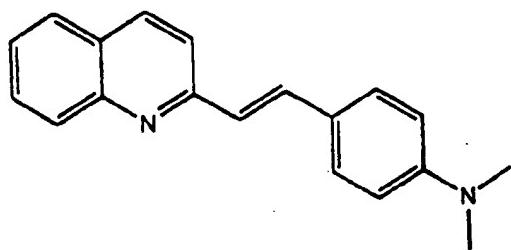


Max : 85 %
EC50 : 1 uM

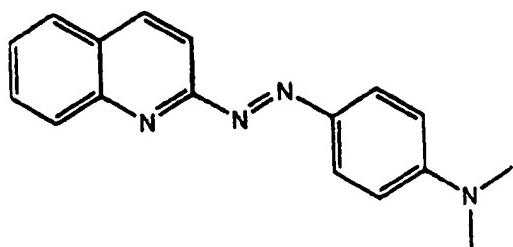
5C

FIG.

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50-0197
Max : 245 %
EC50 : 3 nM



59-0078
Max : 380 %
EC50 : 1 nM

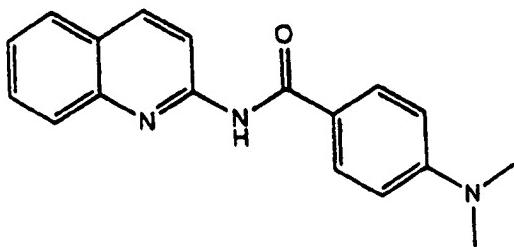
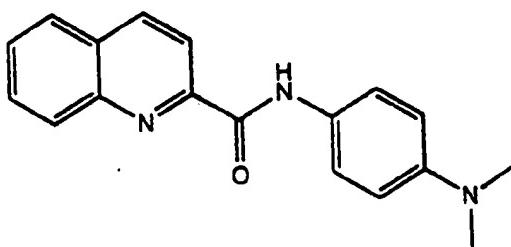
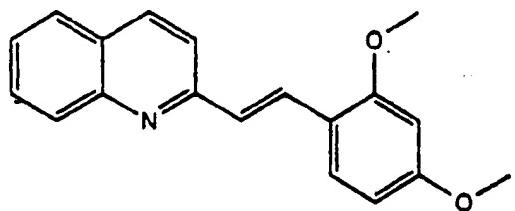
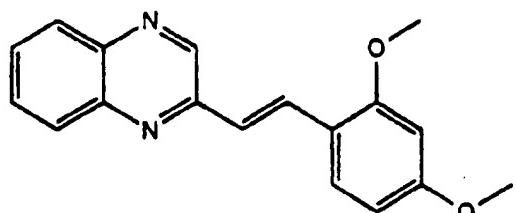


FIG. 6A

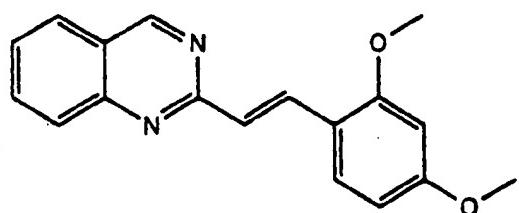
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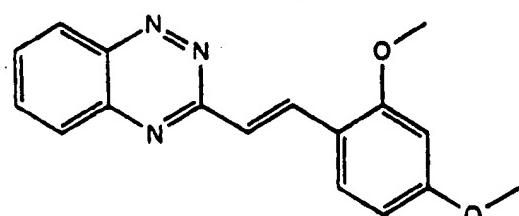
59-0199
Max : 170 %
EC50 : 100 nM



59-0203
Max : 275 %
EC50 : < 1 nM



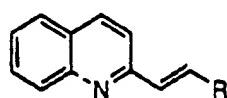
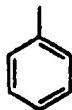
59-0286
Max : 160 %
EC50 : 300 nM



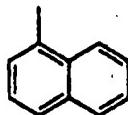
59-0285
Max : 200 %
EC50 : 30 nM

6B
FIG.

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 $\text{R} =$ 

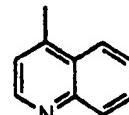
59-0030
Max : 90 %
EC50 : 1 uM



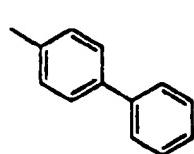
59-0089
Max : 120 %
EC50 : 5 uM



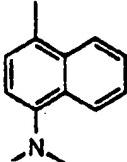
59-0093
Max : 35 %



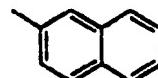
59-0094
Max : 45 %



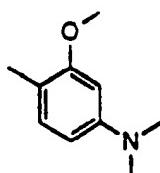
59-0091
Max : 96 %
EC50 : 1 uM



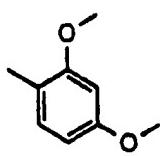
59-0090
Max : 41 %



59-0092
Max : 50 %
EC50 : 10 uM



59-0150
Max : 500 %
EC50 : 1 nM



59-0199
Max : 170 %
EC50 : 100 nM

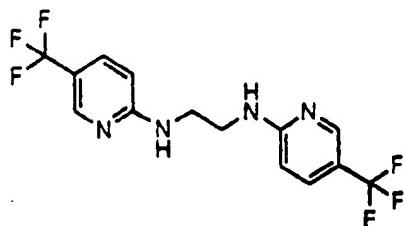


59-0198
Max : 135 %
EC50 : 100 nM

FIG.

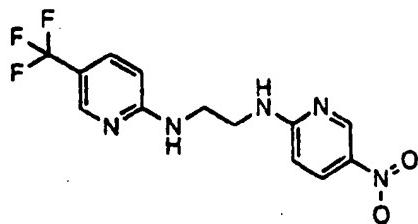
6C

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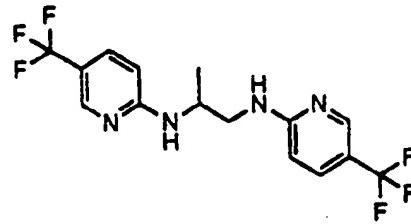
59-0145

Max : 300 %
EC50 : 0.5 uM



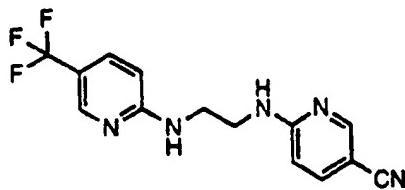
59-0450

Max : 270 %
EC50 : 5 uM



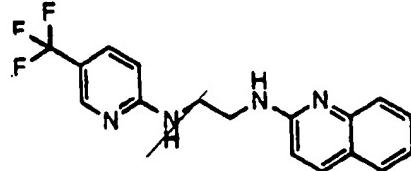
59-0459

Max : 180 %
EC50 : 5 uM



59-0483

Max : 260 %
EC50 : 3 uM



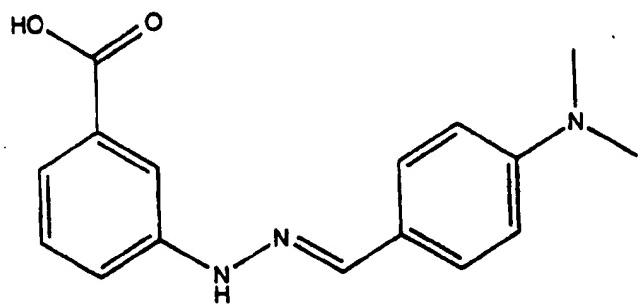
59-0480

Max : 180 %
EC50 : 5 uM

7

FIG.

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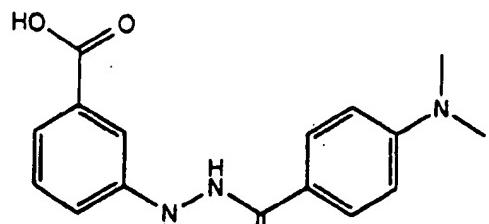


59-0045

 $E_{CSO} = 5nM$

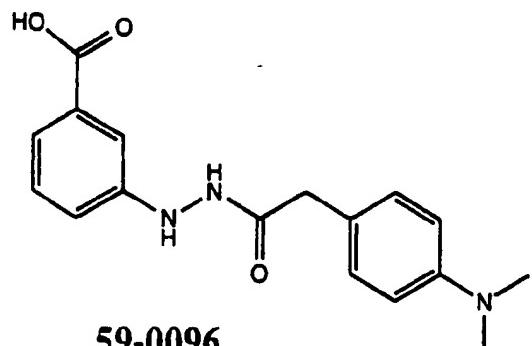
FIG. 8A

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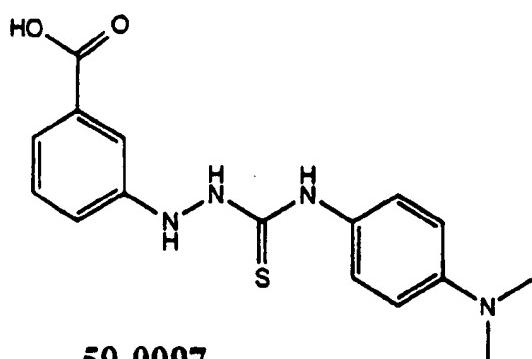
59-0095

Max : 48 %
EC50 : 30 μ M



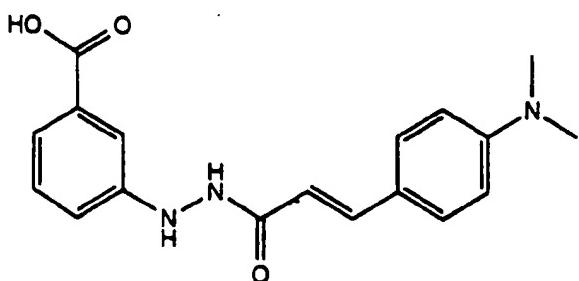
59-0096

Max : 413 %
EC50 : 93 nM



59-0097

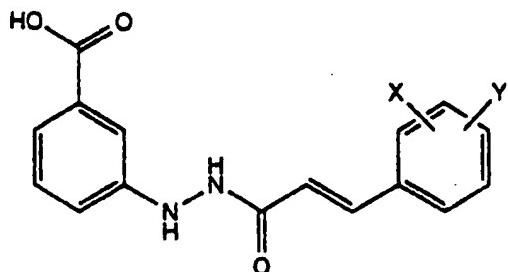
Max : 202 %
EC50 : 100 nM



59-0098

86

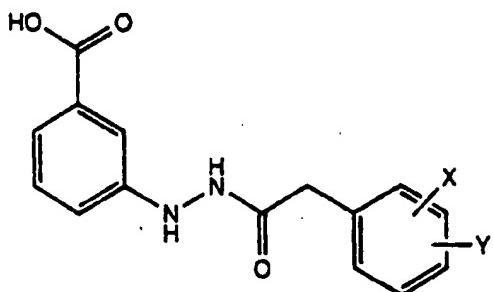
FIG.



X, Y = F, Cl, OMe

< 50 % max @ 100 uM

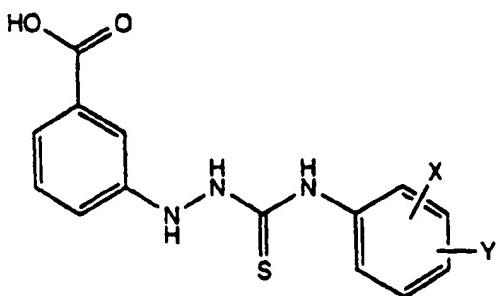
59-0098 Analogs



X, Y = F, Cl, OMe

< 50 % max @ 100 uM

59-0096 Analogs



X, Y = F, Cl, OMe

< 50 % max @ 100 uM

59-0097 Analogs

8C

FIG.

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Compound	Compound Class	EC50	Max Response of 59-0008	ZGI Score in Ex Vivo Assay	Score	
					OS Screen in Ex Vivo Assay	
59-0364	P	0	0	1		
59-0076	P	0	0	1		
59-0451	P	0	0	1		
59-0472	P	0	0	1		
59-0073	P	0	0		1+	
59-0095	H	??	0.5x (30 uM)			1
59-0471	P	??	0.5x (100 uM)	1		
59-0030	Q	??	.7x (1uM)	1		1,1+
59-0470	P	50 uM	1.2x (100 uM)	1		
59-0450	P	5 uM	2.7x (30 uM)			
59-0459	P	5 uM	2x (10 uM)	1		
59-0064	Q	3 uM	1.5x (? uM)	1		

59-0008	Q	1 uM			1
59-0145	T	150 nM	2x (10 uM)		
59-0106	T	300 nM	2x (9 uM)		1
59-0070	T	200nM	2x (3 uM)		1,1+
59-0097	H	100 nM?	2x (30 uM)		1+
59-0096	H	100 nM?	4x (100 uM)		1
59-0116	H	30 nM	2.5x (3 uM)		1+,2-
59-0210	T	30 nM	2x (3 uM)		1
59-0098	Q	20 nM	2x (9 uM)	1+,2-	1+,2-
59-0119	Q	10 nM	2.5x (300 nM)	1+,2-	1,1+
59-0078	Q	9 nM	4x (1 uM)		1
59-0045	H	5 nM	4x (1uM)	1	1
50-0197	Q	3 nM	2.5x (300 nM)	1	1+,2-
59-0099	T	2 nM?	3x (1 uM)		1,1+
59-0282	Q	1 nM	2x (3 uM)		1+,2-
59-0203	Q	1 nM	2x (3 uM)		
59-0072	T	300 pM	2x (uM)	1-1+	1,1+
59-0150	Q	<1 nM	5x (3 uM)	1-2?	1
59-0104	T	<1 nM	2x (uM)	1+,2-	1
59-0103	T	<1 nM	2x (30 nM)		1,1+
59-0124	T	<1 nM	2.5x (1 uM)		1+,2-
59-0205	T	<1 nM	2x (2 nM)		1

H = Hydrazine/Hydrazide (45) T = Benzothiazole (104)

Q = Quinoline/Quinoxaline (197)

P = Bis-pyridines (145)

Figure 9

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Tx-3A: Lumbar vertebra
% Cancellous bone vol

██████	Sham
████	Ovx
████████	Ovx/0145, 5 ug/kg/d
██████████	Ovx/0145, 50 ug/kg/d

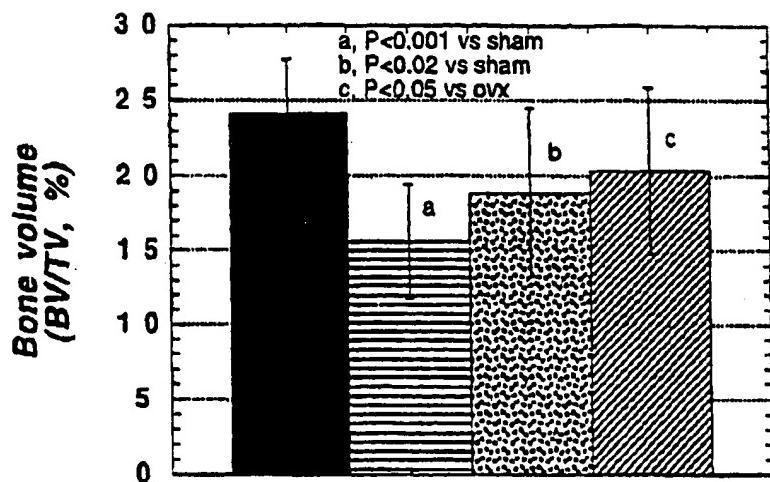
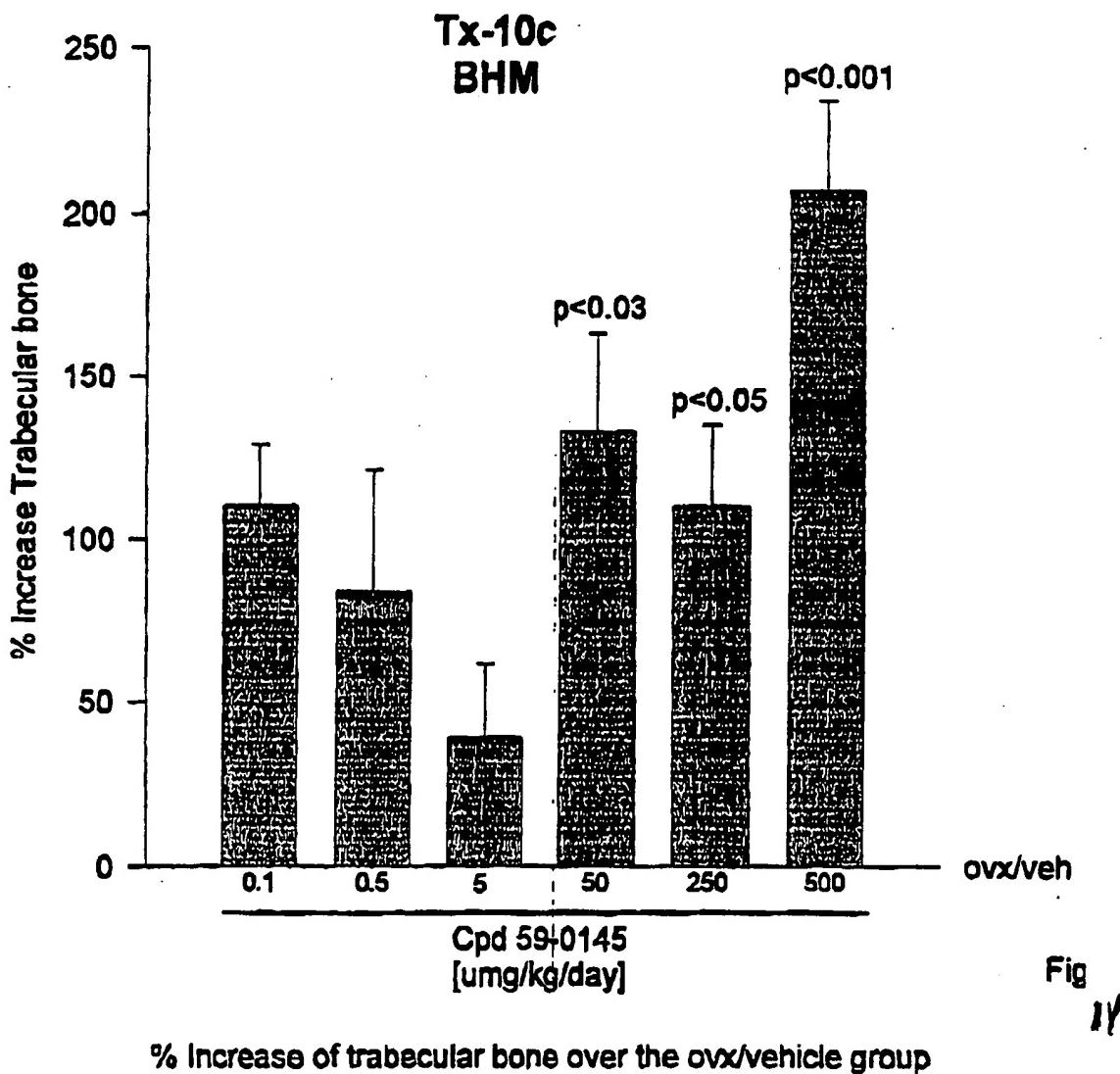


Fig 10

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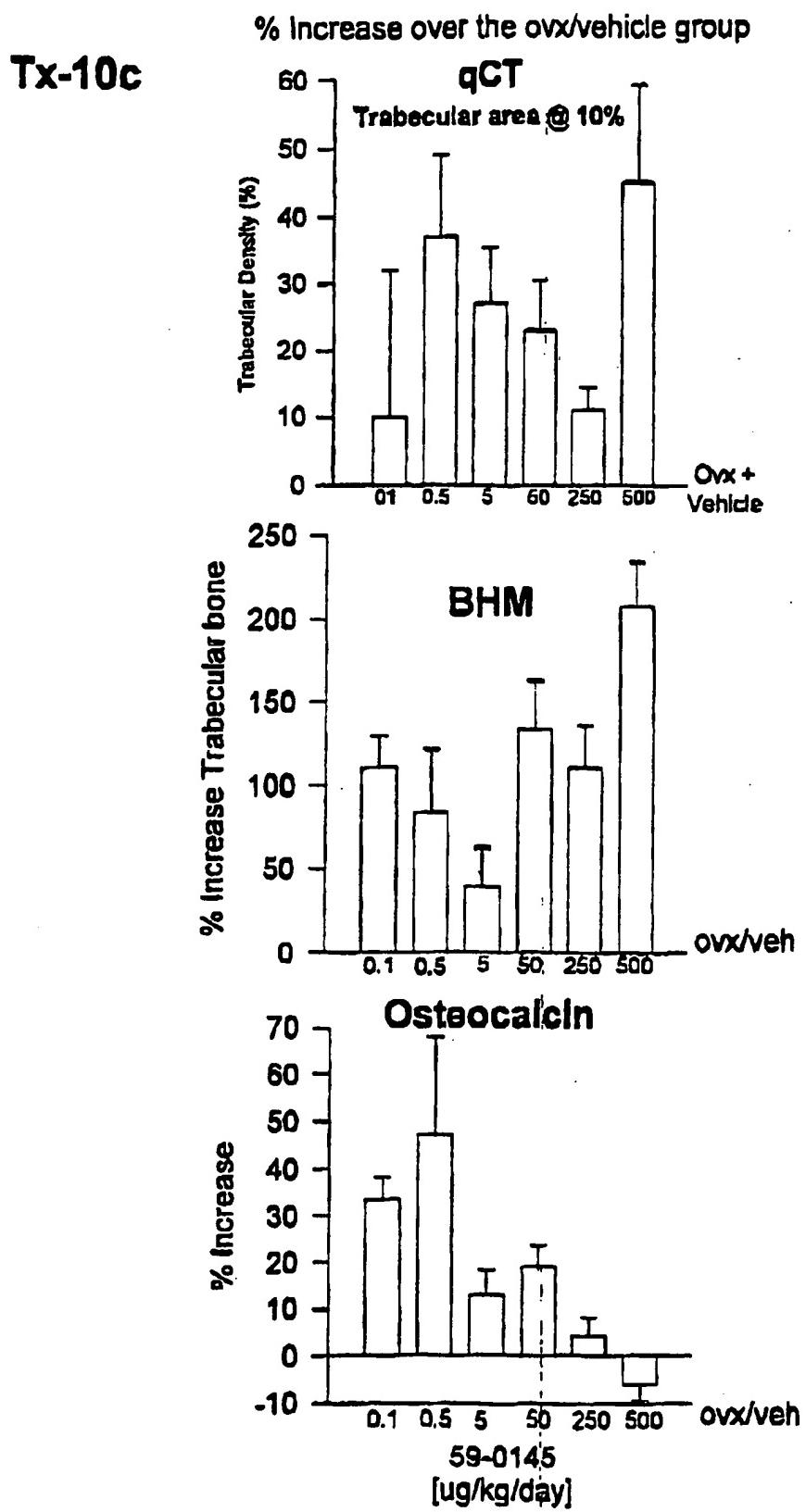


Fig 12

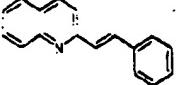
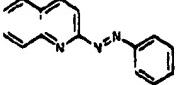
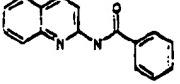
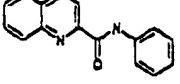
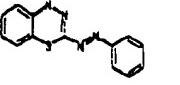
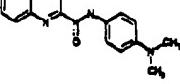
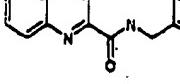
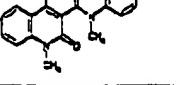
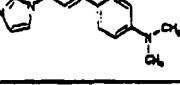
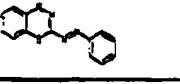
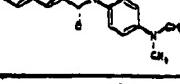
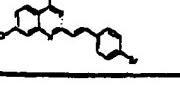
nand2

MOLSTRUCTURE	MOL>NNC MOL WEIGHT NUM1		
	59-0020	266.732	
	59-0021	284.723	
	59-0022	266.367	
	59-0023	239.276	
	59-0008	254.315	
	59-0024	220.276	
	59-0025	224.308	
	59-0026	248.29	
	59-0027	250.303	
	59-0028	226.283	
	59-0029	249.272	

Figure 13
Page 1

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nand2

	59-0031	231.3	
	59-0030	233.275	
	59-0032	248.287	
	59-0033	248.287	
	59-0034	268.343	
	59-0035	291.356	
	59-0036	262.314	
	59-0037	308	
	59-0038	241.295	
	59-0039	312.352	
	59-0040	290.368	
	59-0041	501.902	

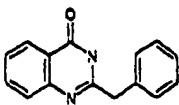
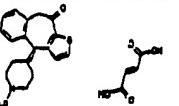
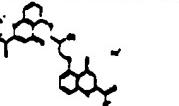
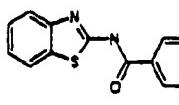
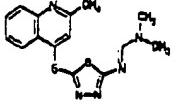
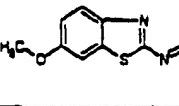
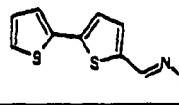
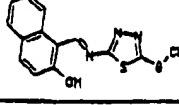
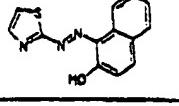
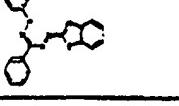
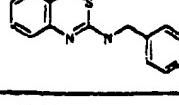
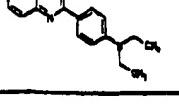
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nand2

	59-0042	281.36
	59-0043	280.288
	59-0044	341.21
	59-0045	283.339
	59-0046	389.372
	59-0047	303.367
	59-0048	384.501
	59-0049	251.29
	59-0050	303.364
	59-0051	251.353
	59-0052	393.276
	59-0053	354.412

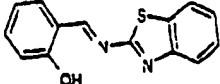
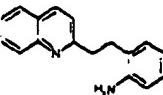
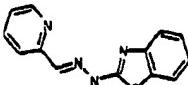
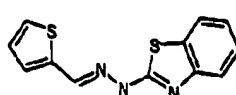
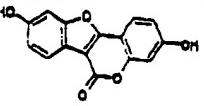
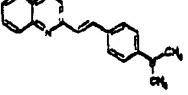
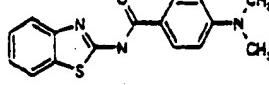
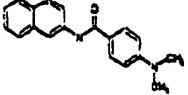
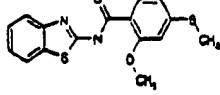
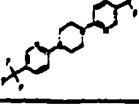
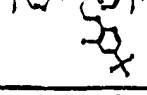
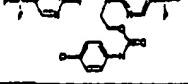
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hand2

	59-0054	236.276
	59-0055	425.508
	59-0056	512.341
	59-0102	284.339
	59-0057	329.448
	59-0058	268.34
	59-0059	375.923
	59-0060	301.391
	59-0061	255.3
	59-0062	357.44
	59-0063	255.344
	59-0064	276.385

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nand2

	59-0065	254.313	
	59-0066	248.33	
	59-0067	254.315	
	59-0068	259.354	
	59-0069	268.223	
	59-0019	275.353	
	59-0070	297.98	
	59-0071	291.352	
	59-0072	330.431	
	59-0073	376.303	
	59-0074	642.735	
	59-0075	616.775	

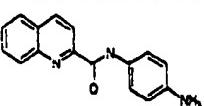
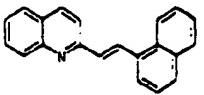
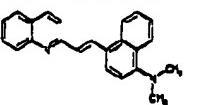
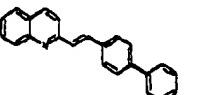
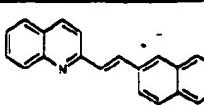
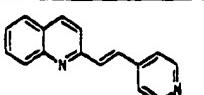
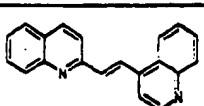
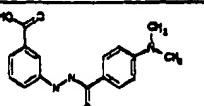
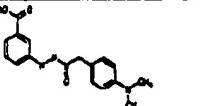
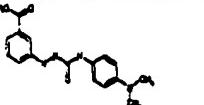
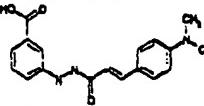
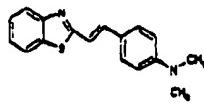
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nand2

<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0076	463.208	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0077	445.193	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0078	276.341	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0079	231.297	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0080	284.338	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0081	377.466	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0082	222.267	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0083	330.414	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0084	264.263	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0085	278.31	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0086	292.293	
<chem>CN1C=CC=C1Cc2cc(C(F)(F)F)c(Cl)c(Cc3cc(O)nc4cc(Cl)c(cc4Cl)c3)cc2Cl</chem>	59-0087	291.309	

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nand2

	59-0088	263.299	
	59-0089	281.357	
	59-0090	324.425	
	59-0091	307.394	
	59-0092	281.357	
	59-0093	232.285	
	59-0094	282.345	
	59-0095	299.328	
	59-0096	313.355	
	59-0097	330.41	
	59-0098	325.368	
	59-0099	280.393	

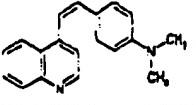
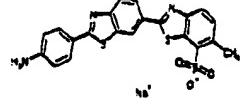
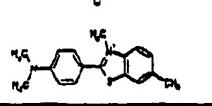
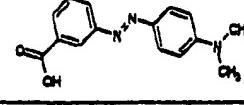
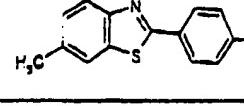
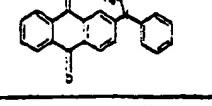
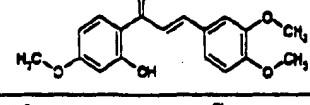
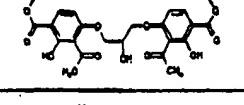
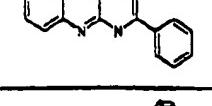
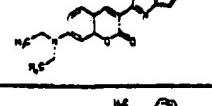
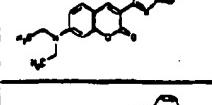
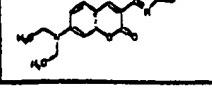
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nand2

<chem>CN1C=CC=C1Cc2ccccc2Cc3ccccc3Cl</chem>	59-0100	254.719	
<chem>CN1CC=CC=C1Cc2ccccc2C(F)(F)F</chem>	59-0101	230.232	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)c3ccccc3S(C)(C)C</chem>	59-0103	313.379	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)c3ccccc3OC(C)C</chem>	59-0104	297.312	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)c3ccccc3OC(C)CO</chem>	59-0105	267.287	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)c3ccccc3OC(C)OC(C)C</chem>	59-0106	297.912	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)C(C)C(O)C(C)C</chem>	59-0107	332.378	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)C(C)C(O)C(C)C(O)C(C)C</chem>	59-0108	316.311	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)C(C)C(O)C(C)C(O)C(C)C(O)C(C)C</chem>	59-0109	316.311	
<chem>CN1C=CC=C1Cc2ccccc2C(=O)C(C)C(O)C(C)C(O)C(C)C(O)C(C)C(O)C(C)C</chem>	59-0110	286.286	
<chem>N#Cc1ccc(cc1)C(=O)O</chem>	59-0111	152.152	
<chem>CN(C)c1ccc(cc1)C=O</chem>	59-0112	149.192	

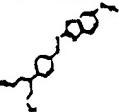
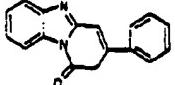
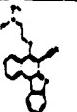
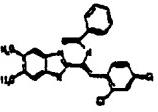
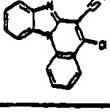
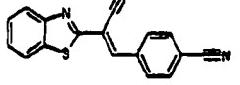
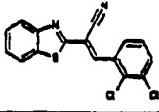
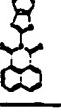
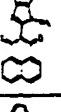
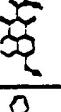
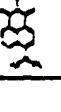
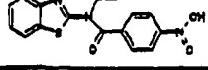
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nand2

	59-0113	274.365	
	59-0114	475.548	
	59-0115	318.87	
	59-0116	269.302	
	59-0117	268.382	
	59-0118	313.354	
	59-0119	314.335	
	59-0120	504.485	
	59-0121	245.284	
	59-0122	333.389	
	59-0123	347.416	
	59-0124	350.44	

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nand2

	59-0125	372.447
	59-0126	260.295
	59-0127	329.405
	59-0128	436.34
	59-0129	277.713
	59-0130	287.345
	59-0131	331.225
	59-0132	313.315
	59-0133	327.342
	59-0134	357.367
	59-0135	356.383
	59-0136	411.868

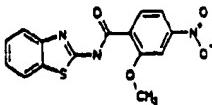
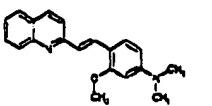
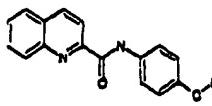
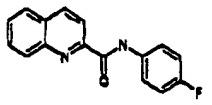
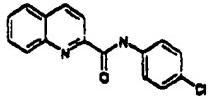
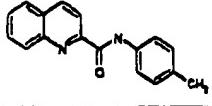
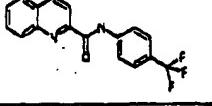
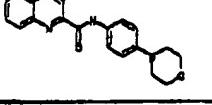
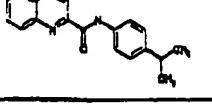
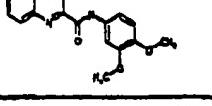
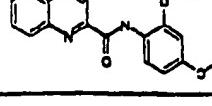
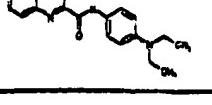
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nand2

<chem>CN1C=CC2=C1C(=O)c1ccccc1-2</chem>	59-0137	296.712	
<chem>CCOC(=O)Cc1ccc(cc1)-c2ccc(Cl)cc2</chem>	59-0138	340.808	
<chem>CCOC(=O)Cc1ccc(cc1)-c2ccc(Cl)cc2</chem>	59-0139	340.424	
<chem>CCOC(=O)Cc1ccc(cc1)-c2ccc(Cl)cc2</chem>	59-0140	289.164	
<chem>CCOC(=O)Cc1ccc(cc1)-c2ccc(Cl)cc2</chem>	59-0141	437.324	
<chem>CCOC(=O)Cc1ccc(cc1)-c2ccc(Cl)cc2</chem>	59-0142	379.288	
<chem>CCOC(=O)Cc1ccc(cc1)-c2ccc(Cl)cc2</chem>	59-0143	447.285	
<chem>CCOC(=O)c1ccc(cc1)-c2ccc(cc2)N3C=CC=CC3S(C)(C)C</chem>	59-0144	316.404	
<chem>CCOC(=O)c1ccc(cc1)-c2ccc(cc2)N3C=CC=CC3S(C)(C)C</chem>	59-0145	350.265	
<chem>CCOC(=O)c1ccc(cc1)-c2ccc(cc2)N3C=CC=CC3</chem>	59-0146	246.268	
<chem>CCOC(=O)c1ccc(cc1)-c2ccc(cc2)N3C=CC=CC3S(C)(C)C</chem>	59-0147	314.364	
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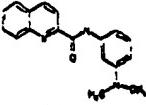
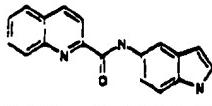
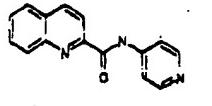
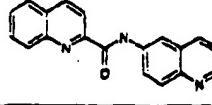
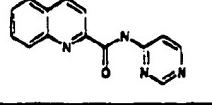
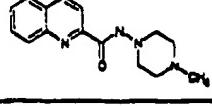
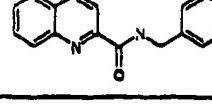
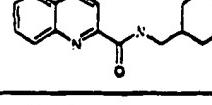
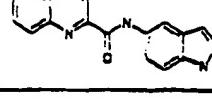
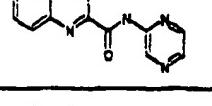
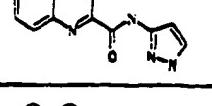
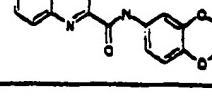
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nand2

	59-0149	329.335	
	59-0150	304.391	
	59-0151	278.31	
	59-0152	266.274	
	59-0153	282.729	
	59-0154	262.311	
	59-0155	316.281	
	59-0156	333.389	
	59-0157	290.384	
	59-0158	308.335	
	59-0159	308.335	
	59-0160	319.406	

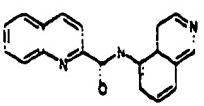
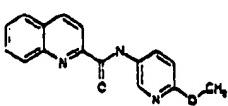
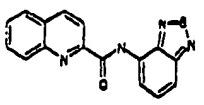
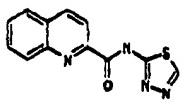
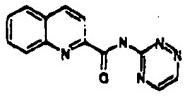
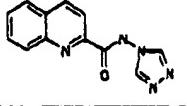
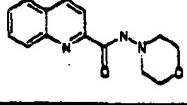
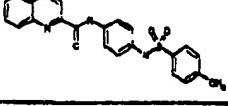
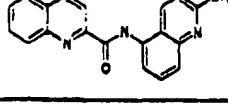
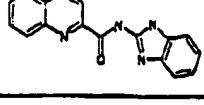
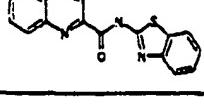
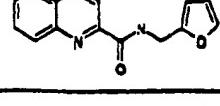
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nand2

	59-0161	291.352
	59-0162	287.321
	59-0163	249.272
	59-0164	299.332
	59-0165	250.26
	59-0166	270.334
	59-0167	263.299
	59-0168	269.346
	59-0169	288.309
	59-0170	250.26
	59-0171	238.249
	59-0172	306.32

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nand2

	59-0173	299.332
	59-0174	279.298
	59-0175	306.348
	59-0176	256.288
	59-0177	251.248
	59-0178	239.267
	59-0179	257.292
	59-0180	417.487
	59-0181	313.358
	59-0182	288.309
	59-0183	305.36
	59-0184	252.272

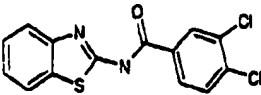
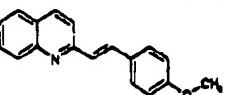
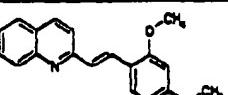
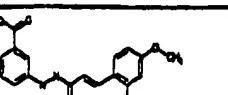
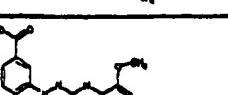
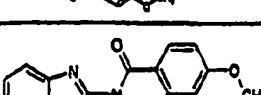
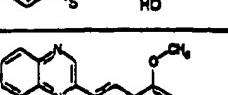
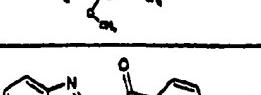
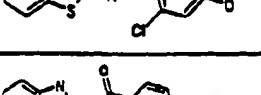
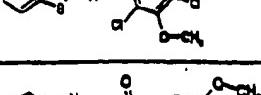
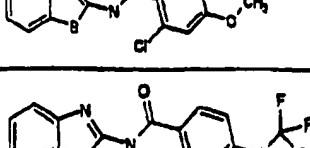
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nand2

	59-0185	345.444	
	59-0186	374.362	
	59-0187	389.494	
	59-0188	616.784	
	59-0189	490.579	
	59-0190	550.631	
	59-0191	584.605	
	59-0192	344.389	
	59-0193	344.389	
	59-0194	344.389	
	59-0195	318.783	
	59-0196	323.202	

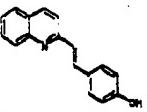
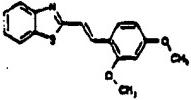
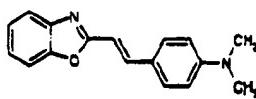
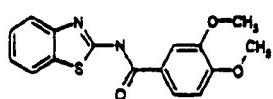
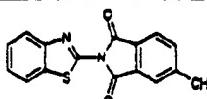
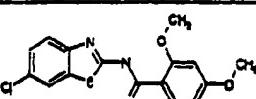
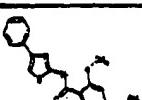
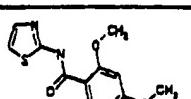
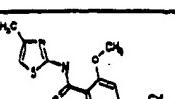
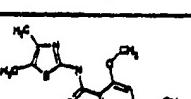
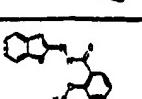
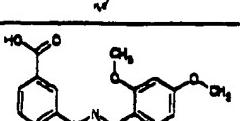
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nand2

	59-0197	323.202	
	59-0198	261.323	
	59-0199	291.348	
	59-0200	342.349	
	59-0201	331.326	
	59-0202	300.337	
	59-0203	292.336	
	59-0204	344.389	
	59-0205	318.783	
	59-0206	348.809	
	59-0207	348.809	
	59-0208	398.308	

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nand2

	59-0209	247.296
	59-0210	297.376
	59-0211	264.326
	59-0212	314.364
	59-0213	294.333
	59-0214	348.809
	59-0215	340.401
	59-0216	264.304
	59-0217	278.331
	59-0218	292.357
	59-0219	329.379
	59-0220	300.312

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hand2

<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)N(c3ccc(O)cc3)C=O</chem>	59-0221	283.329	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C=O</chem>	59-0222	309.367	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)O</chem>	59-0223	284.27	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)c3ccc(O)cc3</chem>	59-0224	330.338	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)O</chem>	59-0225	256.26	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)[O-]</chem>	59-0226	285.258	
<chem>Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)c3ccc(O)cc3</chem>	59-0227	296.398	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)O</chem>	59-0228	269.946	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)O</chem>	59-0229	239.32	
<chem>O=Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)O</chem>	59-0230	284.317	
<chem>O=C(N)Cc1ccc(cc1)-c2cc(N(C)C)c(cc2)C(=O)O</chem>	59-0231	318.399	
<chem>CN1C=NC2=C1C(=O)N(C)Cc3ccc(cc3)-c4cc(N(C)C)c(cc4)N2C</chem>	59-0232	269.35	

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nand2

	59-0233	232.285	
	59-0234	281.31	
	59-0235	251.284	
	59-0236	280.325	
	59-0237	328.39	
	59-0238	340.401	
	59-0239	330.338	
	59-0240	347.393	
	59-0241	344.753	
	59-0242	291.286	
	59-0243	455.334	
	59-0244	414.935	

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nand2

	59-0245	419.887	
	59-0246	675.856	
	59-0247	533.385	
	59-0248	247.296	
	59-0249	298.297	
	59-0250	332.742	
	59-0251	386.426	
	59-0252	361.376	
	59-0253	348.809	
	59-0254	328.39	
	59-0255	376.455	
	59-0256	361.376	

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nand2

	59-0257	348.809	
	59-0258	344.389	
	59-0259	332.354	
	59-0260	344.389	
	59-0261	354.423	
	59-0262	398.36	
	59-0263	368.455	
	59-0264	383.254	
	59-0265	393.26	
	59-0266	328.39	
	59-0267	364.423	
	59-0268	358.416	

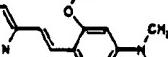
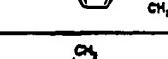
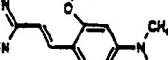
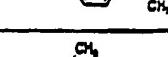
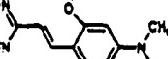
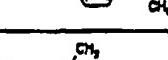
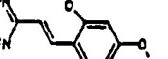
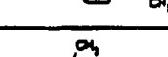
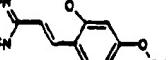
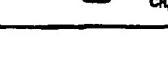
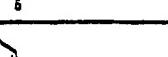
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nand2

<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0269	342.417	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0270	328.39	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0271	360.364	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0272	361.838	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0273	345.445	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0274	329.379	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0275	328.39	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0276	358.373	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0279	327.406	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0277	372.375	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0278	372.375	
<chem>*c1cc2c(cc1[nH]2C(=O)c3ccc(O*)cc3)C(=O)c4ccc(O*)cc4</chem>	59-0280	294.352	

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nand2

	59-0281	310.419
	59-0282	305.379
	59-0283	306.367
	59-0284	305.379
	59-0285	283.324
	59-0286	282.336
	59-0287	306.32
	59-0288	278.357
	59-0289	351.188
	59-0290	351.188
	59-0291	342.949
	59-0292	372.375

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nand2

	59-0293	342.349	
	59-0294	316.278	
	59-0295	312.323	
	59-0296	316.743	
	59-0297	329.31	
	59-0298	298.297	
	59-0299	304.308	
	59-0300	236.269	
	59-0301	326.35	
	59-0302	285.733	
	59-0303	275.31	
	59-0304	469.178	

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nand2

<chem>Cc1ccc(cc1)C(=O)c2cc3c(cc2S(=O)(=O)c4cc5c(c4)oc(=O)c5)oc(=O)c3</chem>	59-0305	340.789
<chem>CC(=O)N1C2=C(C=C1Cc3ccccc3)SC(=O)N=C2Cc4ccccc4</chem>	59-0306	308.403
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)oc(=O)c2</chem>	59-0307	300.38
<chem>CC(=O)c1ccc2c(c1)oc(=O)c2</chem>	59-0308	304.27
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)OCc4ccccc4</chem>	59-0309	330.406
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)OCc4ccccc4</chem>	59-0310	368.378
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)Nc4ccccc4</chem>	59-0311	287.705
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)c4ccccc4</chem>	59-0313	293.127
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)c4ccccc4</chem>	59-0314	343.134
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)c4ccccc4</chem>	59-0315	275.137
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)c4ccccc4</chem>	59-0316	303.191
<chem>CC(=O)c1cc2c(cc1Nc3ccccc3)C(=O)c4ccccc4</chem>	59-0317	377.579

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nand2

	59-0318	326.6791	
	59-0319	282.345	
	59-0320	206.247	
	59-0321	256.691	
	59-0322	284.745	
	59-0323	285.143	
	59-0324	234.301	
	59-0312	309.582	
	59-0325	424.505	
	59-0326	404.543	
	59-0327	390.517	
	59-0328	418.57	

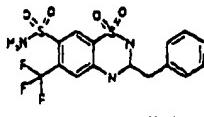
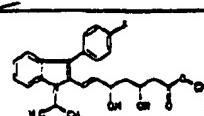
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nand2

	59-0329	424.53	
	59-0330	411.47	

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nand2

	59-0354	421.419
	59-0342	425.497

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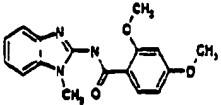
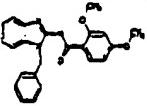
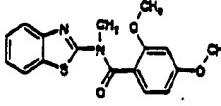
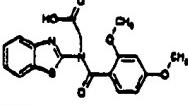
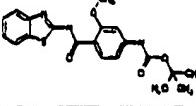
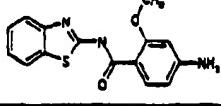
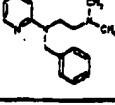
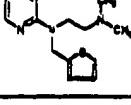
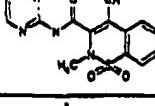
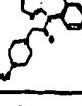
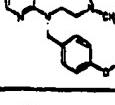
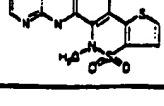
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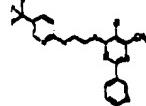
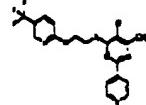
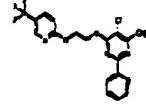
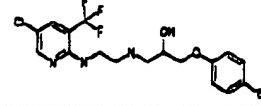
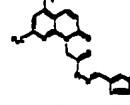
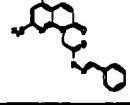
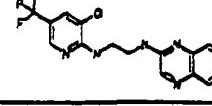
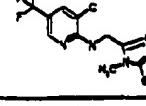
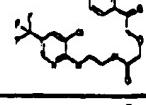
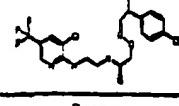
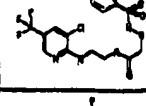
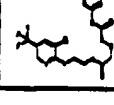


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	59-0363	216.247	
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	59-0366	384.357	
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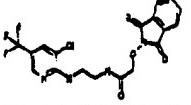
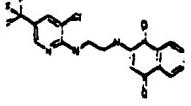
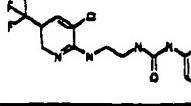
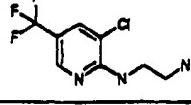
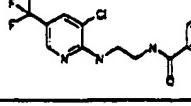
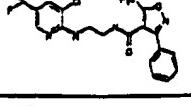
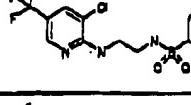
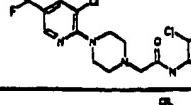
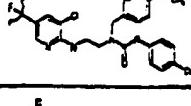
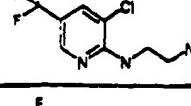
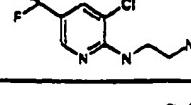
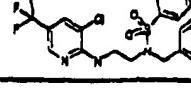
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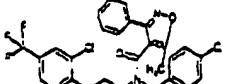
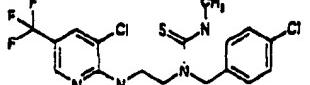
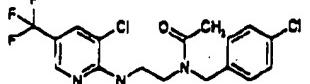
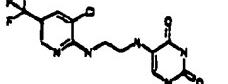
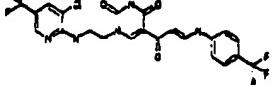
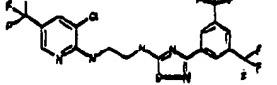
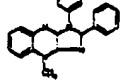
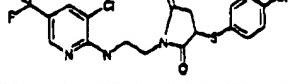
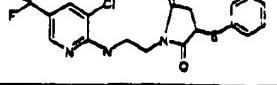
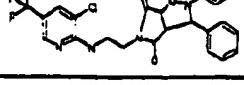
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nand2

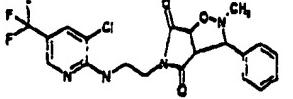
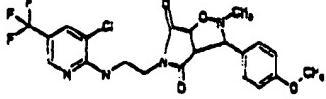
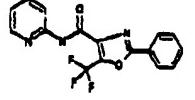
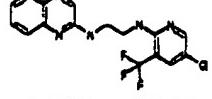
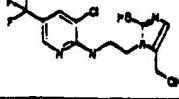
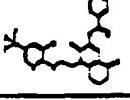
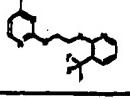
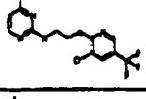
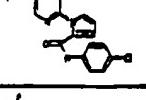
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nand2

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	59-0442	303.704
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	59-0450	329.281
	59-0451	384.71

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nand2

<chem>CN1C=CC=C1Cc2ccc(C)cc2</chem>	59-0452	242.324
<chem>Cc1ccc(C)cc2ccc(NCc3ccccc3)cc12</chem>	59-0453	214.271
<chem>Cc1ccc(C)c2ccc(NCc3ccccc3)cc12</chem>	59-0454	264.291
<chem>Cc1ccc(C)c2ccc(NCc3ccccc3)cc12</chem>	59-0455	300.32
<chem>Cc1ccc(C)c2ccc(NCc3ccccc3)cc12</chem>	59-0456	308.296
<chem>CC(=O)N1Cc2ccc(C)cc2Cc3ccc(C)cc13</chem>	59-0457	330.342
<chem>CC(=O)N1Cc2ccc(C)cc2Cc3ccc(C)cc13</chem>	59-0458	300.408
<chem>CC(=O)N1Cc2ccc(C)cc2Cc3ccc(C)cc13</chem>	59-0459	364.292
<chem>CC(=O)N1Cc2ccc(C)cc2Cc3ccc(C)cc13</chem>	59-0460	252.238
<chem>CC(=O)N1Cc2ccc(C)cc2Cc3ccc(C)cc13</chem>	59-0461	286.265
<chem>CC(=O)N1Cc2ccc(C)cc2Cc3ccc(C)cc13</chem>	59-0462	280.292
<chem>CC(=O)N1Cc2ccc(C)cc2Cc3ccc(C)cc13</chem>	59-0463	253.226

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<chem>CN(C)c1ccc(cc1)Cc2ccccc2Cc3ccccc3</chem>	59-0464	267.253	
<chem>CC(=O)c1ccc(cc1)Cc2ccccc2Cc3ccccc3</chem>	59-0465	363.26	
<chem>CC(=O)c1ccccc1Cc2ccccc2Cc3ccccc3</chem>	59-0466	315.352	
<chem>CC(=O)c1ccccc1Cc2ccccc2Cc3ccccc3</chem>	59-0467	212.294	
<chem>CC(=O)c1ccccc1Cc2ccccc2Cc3ccccc3</chem>	59-0468	213.289	
<chem>CC(=O)c1ccccc1Cc2ccccc2Cc3ccccc3</chem>	59-0469	378.318	
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<chem>CC(=O)c1ccccc1Cc2ccccc2Cc3ccccc3</chem>	59-0471	350.261	
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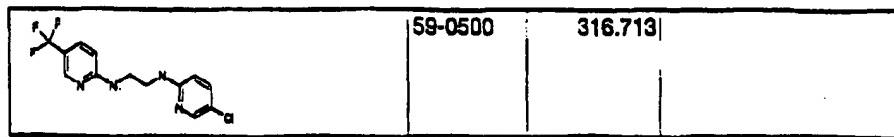
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nand2

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	59-0495	299.294
	59-0496	354.33
	59-0497	340.303
	59-0498	282.268
	59-0499	296.294

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nand2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18864

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS--structure

APS--diaryl, bone, osteo?, BMP

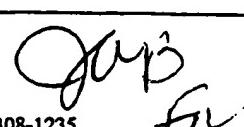
DIALOG--diaryl, bone, osteo?, BMP

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,441,964 A (BRYANT et al.) 15 August 1995, see entire document.	1-2, 5-28, 55-56
Y	US 5,523,309 A (BRYANT et al.) 04 June 1996, see entire document, especially claim 8.	1-2, 5-28, 55-56
Y,P	US 5,622,974 A (MUEHL) 22 April 1997, see entire document, especially claim 5.	1-2, 5-28, 55-56
Y	WO 93/10113 A1 (TEIKOKU HORMONE MFG. CO., LTD.) 27 May 1993, see entire document.	1-2, 5-28, 55-56
Y	WO 95/10513 A1 (PFIZER INC.) 20 April 1995, see entire document, especially claim 20.	1-2, 5-30, 55-56
Y	US 5,280,040 A (LABROO et al.) 18 January 1994, see entire document.	1-4, 31-43, 55-56

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance		
"B" earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"Z"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 JANUARY 1998	Date of mailing of the international search report 26 FEB 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CELIA CHANG Telephone No. (703) 308-1235 

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/18864

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr. Vol. 127, abstract No. 127:17703, PETRIE et al. 'Preparation of (hetero) aromatic compounds for treating bone deficit conditions', WO-97/15308 (Eng.).	1-4, 31-43, 55-56
Y	Chem. abstr. Vol. 107, abst. No. 107:109578, WATTS et al. 'Studies on the ligand specificity and potential identity of microsomal antiestrogen-binding sites', Mol. Pharmacol. 1987, 31(5), 541-51.	1-2, 50-56
Y	Chem. abstr. Vol. 108, abstract No. 108:69162, JORDAN et al. 'Effects of antiestrogens on bone in castrated and intact female rats', Breast Cancer Res. Treat. 1987, 10(1), 31-5.	1-2, 50-56
Y	Chem. abstr. Vol. 115, abstract No. 115:8533, SCHWARZ et al. '1,2-diphenyl-1-pyridybut-1-enes - potential antiestrogens. part 1. synthesis' Arch. Pharm. 1991, 324(4), 223-9.	1-2, 44-49, 55-56
Y	NEELAM et al. Structure-activity relationship of antiestrogens: A study using triarylbutenone, benzofuran and triarylfuran analogues as models for triarylethylenes and triarylpropenones. J. Med. chem. 1989, Vol. 32, pages 1700-1707, see entire article.	1-2, 50-56
Y	VON ANGERER et al. Studies on heterocycle-based pure estrogen antagonists. Ann. N. Y. Academy Sciences. 1995, Vol. 761, pages 176-191, see especially pages 178-180.	1-2, 5-28, 55-56

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/18864

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/18864

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): A61K 31/165, 31/215; 31/33, 31/405, 31/415, 31/42, 31/425, 31/44, 31/47, 31/505, 31/53, 31/535, 31/54

A. CLASSIFICATION OF SUBJECT MATTER:

US CL : 514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/222.5, 223.2, 223.8, 224.2, 226.5, 229.2, 230.5, 255, 258, 259, 296, 307, 311, 336, 345, 352, 354, 457, 365, 367, 374, 375, 385, 394, 396, 397, 415, 443, 535, 646

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The claims are deemed to correspond to the species as listed in the following manner:

Group I, claims 3-4 and 31-43 compounds corresponding to Ar1 is condensed six membered heterocyclic ring, Ar2 is various aromatic rings;

Group II, claims 5-28, compounds corresponding to Ar1 is condensed five membered heterocyclic ring, Ar2 is various aromatic rings;

Group III, claims 29-30, compounds corresponding to Ar1 is isolated five membered heterocyclic ring, Ar2 is various aromatic rings;

Group IV, claims 44-49, compounds corresponding to Ar1 is isolated six membered heterocyclic ring, Ar2 is various aromatic rings;

Group V, claims 50-54, compounds corresponding to Ar1 is phenyl ring, Ar2 is various aromatic rings;

Group IV, claims 1-2, 55-56 in part (remaining compounds)

The following claims are generic: 1-2, 55-56

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2 and ANNEX B section (f), the species lack the same or corresponding special technical features for the following reasons:

The six groups of compounds corresponding to method of treating conditions of deficiency in bone growth, resorption or replacement using structurally distinctive compounds. Each group of compounds as delineated above does not share significant structural element (see Ar1, Ar2 and L are all variables, thus, not common element). In addition, at least one Markush alternative is found in CA 127:17703.